DRINKING WATER AND CANCER:

REVIEW OF RECENT FINDINGS AND ASSESSMENT OF RISKS

Prepared by
Science Research Systems, Inc.

For the
Council on Environmental Quality

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Executive Summary

During the past decade concern over possible cancer risks to humans from organic contaminants in drinking water led to studies to measure these contaminants and to estimate their effects on human cancer risks. Much of the initial concern focused on chlorinated organic contaminants (including particularly the four trihalogenated methanes (THMs): chloroform, bromoform, bromodichloromethane and dibromochloromethane) formed during the chlorination of water to destroy harmful bacteria. More recently, high concentrations of synthetic organic chemicals have been discovered in untreated drinking water from ground water sources in certain areas of the United States. Some of these chemicals are known to cause cancer in laboratory animals.

In 1977 a committee of the National Academy of Sciences reviewed the completed epidemiological studies of the association between water quality and human cancer risk. Most of these studies were of a type known in the epidemiological literature as ecological studies. Such studies are primarily useful for generating hypotheses to be tested by more detailed epidemiological studies. Within the past two years more detailed studies, known as case control studies, have been completed in Illinois, Louisiana, New York, North Carolina, and Wisconsin. None of the epidemiological studies completed to date have investigated putative cancer risks associated with recently discovered synthetic organic contaminants in drinking water from ground water sources.

It is the purpose of this report to assess the current evidence of cancer risks to humans from organic contaminants in drinking water. First, we review the epidemiological literature with particular emphasis upon the recently

completed case control studies. We consider the strength of this epidemiologic evidence for determining if organic contaminants in drinking water have caused cancer in humans. Next, we use animal data to estimate the carcinogenic potencies of synthetic organic chemicals recently identified as contaminants of drinking water from some ground water sources. These potency estimates are used to quantify the possible ranges of risks from untreated drinking water from some highly polluted wells. Finally, we discuss areas in which future research is needed. Our major conclusions are as follows:

1. The recently completed case control studies have strengthened the evidence for an association between rectal, colon and bladder cancer and drinking water quality provided by the earlier epidemiological studies reviewed by the National Academy of Sciences committee. While the epidemiological studies completed to date are not sufficient to establish a causal relationship between chlorinated organic contaminants in drinking water and cancer, they do contain evidence which supports such a relationship for rectal cancer and, to a lesser extent, for bladder and colon cancer.
2. Putative increases in cancer risks associated with organic contaminants in drinking water appear to lie near the lower limit of what can be reliably detected by epidemiological methods.
3. No clear trend of increasing cancer risk with increasing exposure to organic contaminants in drinking water has been demonstrated by the studies conducted to date although evidence suggestive of such trends has been obtained for rectal cancer in one study and for colon cancer in another study.

4. Concentrates of chlorinated nonvolatile organic compounds in drinking water have been found to be mutagenic in mammalian cells and to be capable of transforming human cells into cells which exhibit some biochemical properties associated with tumor cells. These results support the hypothesis that chlorinated nonvolatile organic compounds in drinking water may be carcinogenic in humans. Most of the nonvolatile organic content of drinking water has not yet been identified.

5. Estimates made from animal data of human cancer risks from lifetime consumption of water from some highly polluted wells are small enough that they would probably not contribute noticeably to existing human cancer rates. However these estimates do not incorporate risks from a) as yet unidentified organic contaminants, b) contaminants identified in ground water but for which no adequate carcinogenicity data exist, or c) possible synergistic effects of organic contaminants in ground water.

The earlier ecological studies reviewed by the National Academy of Sciences in 1977 compared aggregate area-wide cancer mortality rates to measures of water quality applicable to those areas. Most of these studies used indirect measures of water quality. For example, cancer rates in populations using chlorinated water were compared with rates in populations using unchlorinated water; similar comparisons were made between populations using surface water and populations using ground water. Cancer of the bladder, stomach, rectum and colon were found to be positively associated with chlorinated water or surface water in a number of geographic areas. In two studies where triihalo-

genated methane concentrations were measured directly, increased rates of bladder cancer were found to be associated with higher chloroform concentrations. One of these studies also mentioned positive associations between chloroform levels and rectal and colon cancer rates. In reviewing these studies, the National Academy of Sciences committee noted that "the association found for bladder cancer was small and had a large margin of error."

In each of the five recently completed case control studies, death certificates were searched to locate the residential addresses of people who had died of gastro-intestinal or urinary tract cancer. The water supplies serving these addresses were then determined along with their chlorination status (chlorinated or unchlorinated) and their source (surface or ground water). Comparable information was obtained for a sample of death certificates from a population who died of other causes. In most of the studies, this control population was chosen to match the population of cancer victims in terms of such factors as sex, race, age and year of death. Using this information for each particular type of cancer, the ratios of cancer risks for those on chlorinated water to cancer risks for those on unchlorinated water were estimated. In four of the studies, the risk ratios for surface water to ground water were also computed for several types of cancer. Each of the studies attempted to account for the confounding influence of other risk factors such as urbanization and occupation. Most of the studies also attempted to account for population migration - either by direct estimation or by selection of a study population in an area of low population mobility.

Rectal cancer risk ratios for chlorinated versus

unchlorinated water* were found to range from 1.13 to 1.93 in the five studies, and in three of the studies the elevation of the risk ratio above 1.00 was statistically significant. Colon cancer risk ratios also exhibited statistically significant elevations in three of the five studies as did bladder cancer risk ratios in two of the studies. Thus, elevated rectal, colon and bladder cancer risks have been found in these case control studies by different investigators and in several geographic areas of the country. Increased risks of rectal, bladder and colon cancer of the magnitudes suggested by these studies are large enough to be of concern but yet small enough to be very difficult to separate from confounding risks associated with other environmental factors.

Three of these studies investigated dose-response effects by attempting to determine whether there were increasing cancer risks with increasing exposure to organic contaminants in drinking water. No clear trend was established. One study showed increasing rectal cancer mortality rates with increasing exposure to surface water. This suggests a dose-response gradient for rectal cancer. In another study, results suggestive of a colon cancer dose-response gradient were found when effects of water purification and rural runoff were taken into account.

The methodologies used in these case control studies represent a considerable refinement over those used in the earlier ecological studies. Linkage of individual residential addresses with their water supplies permitted improved measures of exposure. In most of the case control studies,

*Such a "risk ratio" roughly estimates the ratio of the risk of rectal cancer for a person using chlorinated water to the comparable risk for a person using unchlorinated water.

migration was taken into account either by selecting study populations from areas with low rates of migration during the past 20 years, or else by using indirect measures of migration based upon place of birth and place of death. In some of these studies, the occupations listed on the death certificates were used to control for possible confounding due to occupation. The Wisconsin study, which found a statistically significant association between colon cancer and drinking water quality, was limited to white females, only 0.56% of whom had been employed in an occupation considered to have a high cancer risk. All but one of the studies controlled for age, race, and sex. The Louisiana study also controlled for ethnic background (Acadian ancestry).

However, these case control studies have some of the same limitations as the earlier ecological studies. The measures of water quality used in the case control studies are essentially the same indirect measures (e.g., chlorinated versus unchlorinated or surface versus ground) that were used in the ecological studies. Use of death certificate data limits the information available to evaluate certain potentially confounding factors. Dietary and smoking habits are not a part of death certificate data. Death certificates only include a recent residential address and the "usual" occupation; detailed residential and occupational histories generally are not available. The latency period between exposure to a carcinogen and diagnosis of cancer is probably at least ten years for gastrointestinal and urinary tract cancer. Thus the water qualities which should be correlated with increased cancer risks in these studies are those to which the subjects were exposed at least 10 years (and probably longer) prior to their deaths. None of the studies completed to date include direct measurements of water

quality during this time period.

A new case control study of bladder cancer is nearing completion and should be subject to fewer limitations than were the epidemiological studies completed to date. This study is based on interview data from over 3000 newly diagnosed cases of bladder cancer and over 6000 controls. In addition, a case control study of colorectal cancer based on interview data from about 450 incident cases and about 900 controls is in progress. Use of interview data should permit controlling for numerous potentially confounding factors which have not been adequately controlled for in studies to date which were based upon death certificates.

Numerous incidents have recently occurred in which drinking water from ground water sources has been found to be contaminated with synthetic organic chemicals at concentrations far above those which previous national surveys have found in either surface water or ground water. These contaminants - consisting of trihalogenated methanes, pesticides, industrial solvents and other organic compounds - include many known or suspected carcinogens. The pollution of ground water is of concern not only because it represents a present health risk, but also because once contaminated, ground water may remain so for decades. Since approximately 50% of the U.S. population relies on ground water for its primary source of drinking water, pollution of ground water is indeed a potentially serious problem. The epidemiological studies completed to date do not permit estimation of risks due to these recently identified organic contaminants in unchlorinated drinking water from ground water sources. In most cases the mixture of chemicals found in highly contaminated ground water is distinctly different from that found in drinking water pertaining to these epidemiological studies.

To estimate risks from chemicals present in ground water, a list of chemical carcinogens known to be present in significant quantities in drinking water wells was compiled. Carcinogenic potencies were estimated for each of these chemicals based upon data from animal bioassays. This was a two-step procedure. First, low dose carcinogenic potencies were estimated from animal data using a method recently adopted for this purpose by the EPA. Next, these animal risk estimates were converted so as to apply to humans using a method based on the relative surface areas of the animal species and humans. These calculated carcinogenic potencies were then used to estimate an upper limit on human risk for each single chemical at the maximum concentration known to be present in drinking water wells in one of the most highly contaminated areas of the country. Finally, all of the risks were added together to estimate an upper limit of the risk from all of the carcinogens identified in these wells. The resulting estimate of lifetime human excess risk was less than 0.1%. Since the national lifetime cancer risks for rectal, colon and bladder cancer are each at least 1%, a lifetime risk of 0.1% would correspond to less than a 10% increase in human cancer risk at any one of these cancer sites.

There are many uncertainties associated with these estimates. The low dose animal potencies were estimated by upper confidence limits calculated from a multistage model which assumes that risk increases linearly with dose for low doses. This procedure is probably more apt to overestimate than underestimate low dose risks. If the linear assumption is not valid, this procedure might greatly overestimate risks from low doses. The procedure used for converting from animal risks to human risks also seems, on the basis of human-animal comparisons made from other chemicals, to tend

to overestimate human risks. However, the data base upon which these human-animal comparisons are made is weak.

On the other hand, only chemicals which have been identified as ground water contaminants and for which adequate carcinogenicity data exist were accounted for in the estimates of risks from these highly polluted wells. High concentrations of other chemicals were present which have not been adequately tested for carcinogenicity and, further, chemicals which have not yet been identified could have a significant carcinogenic effect. It is also possible that the contaminants in these wells could act synergistically to collectively produce a carcinogenic effect which is larger than that suggested by animal studies on individual chemicals. No data were available that would permit the possibility of such synergistic action to be taken into account in the risk estimates.

Directions for Future Research

1. Case control studies based upon interview data from newly diagnosed cases of rectal, bladder and colon cancer are needed. Such studies should relate cancer risks to lifetime water quality histories while controlling for the potentially confounding effects of smoking, diet, coffee drinking, artificial sweetener consumption, alcohol consumption, migration, occupational history and other environmental exposures. Water quality measurements should include as complete a characterization of the organic contaminants as practical, as well as measurements of other contaminants such as nitrates and radionuclides. At least a thousand cases at each site should be included so as to provide some assurance of detecting risk ratios around 1.3. It should be noted that a large case control study based on interview data from newly diagnosed cases of bladder cancer and satisfying many of the

above conditions is nearing completion. In addtion, a case control study based on interview data from over 450 colorectal cancer cases is in progress.

2. Further studies of the identities, carcinogenicity, mutagenicity, mode of formation and practical methods of removal are needed for the organic contaminants in drinking water.

CHAPTER I

INTRODUCTION

During the past decade concern over the possible association between organic contaminants in drinking water and increased rates of human cancer led to studies to measure levels of organic contaminants in drinking water and to estimate their possible effects on human cancer risks. Much of the initial work on cancer risks from drinking water has focused on chlorinated surface water, which usually contains trace quantities of the four trihalogenated methanes (THMs) - chloroform, bromoform, bromodichloromethane, and dibromochloromethane. These compounds are formed during water chlorination by the action of chlorine and bromine on organic precursors, which are believed to consist mainly of naturally occurring soil humic acids. As noted in the 1977 survey of drinking water and health by the National Academy of Sciences (NAS, 1977), over 90% of the total organic content of drinking water has not yet been identified. The National Organics Reconnaissance Survey (NORS) (EPA, 1975) found that THM levels are usually (but not invariably) higher in surface water than in ground water and in chlorinated water than in unchlorinated water. On the basis of this work, unchlorinated ground water has often been regarded as the standard of unpolluted water, against which water from other sources can be compared.

Over the past two years numerous incidents have occurred in which ground water has been found to be contaminated with synthetic organic chemicals other than THMs at levels far above those seen in surface water or ground water in previous national surveys. The contaminants, consisting of pesti-

cides, industrial solvents, chloroform, and other synthetic organic compounds, include many known or suspected human and animal carcinogens. The pollution of ground water is of concern not only because of present health risks, but also because once contaminated, ground water may remain so for many decades. Since approximately 50% of the U.S. population relies on ground water for its primary source of drinking water (EPA, 1980c), pollution of ground water is indeed a potentially serious problem.

The purpose of this report is twofold. First, we review the epidemiological literature on cancer risk associated with organic contaminants in drinking water, with particular emphasis on recently completed case control studies. These studies compare estimated cancer risk associated with chlorinated surface water as compared to ground water but do not permit estimation of risks due to some recently identified organic pollutants in ground water. Second, we use animal data to estimate human cancer risks associated with chemicals which have been identified in ground water. In conclusion, we discuss the types of studies in progress and comment on the additional work needed.

CHAPTER II

REVIEW OF EPIDEMIOLOGICAL STUDIES

Introduction

This chapter reviews the epidemiological studies completed to date on the association between drinking water quality and cancer. These studies may be classified as either ecological studies or case control studies. Ecological studies compare cancer rates in different groups of people to aggregate measures of exposure applied to these groups. Such studies are primarily descriptive and useful in formulating hypotheses. Case control studies, on the other hand, relate exposure levels experienced by people with the disease (cases) to exposure levels experienced by people without the disease (controls). Such studies relate risk estimates to individual exposure patterns and are used to test hypotheses suggested by ecological studies.

Until recently, most of the evidence on the relationship between water quality and cancer came from ecological studies. Over the past year, however, a number of new case control studies have been completed. Thus it seems particularly appropriate at this time to review the accumulated evidence. The first part of this chapter discusses the ecological studies, most of which have been previously reviewed by Wilkins et al. (1979), Shy and Struba (1980), Hoel and Crump (1979), and a committee of the National Academy of Sciences (NAS, 1978 and 1980).[1]

[1]The recently issued study by the National Academy of Sciences on drinking water and health (NAS, 1980) includes a review of epidemiological studies completed through 1978.

The second part of the chapter discusses the five major case control studies completed to date. These are the studies by Alavanja et al. (1978), Brenniman et al. (1980), Kanarek and Young (1980), Gottlieb et al. (1980 a,b), and Struba (1979). Since only the study by Alavanja et al. (1978) has been discussed in published review articles, these five studies are discussed here in more detail than are the ecological studies.

Ecological Studies

From 1974 to 1979 a number of epidemiological studies were conducted using ecological study designs, in which aggregate (e.g., county average) site-specific cancer mortality rates were compared to aggregate water quality measures (e.g., fraction of the county population using surface water). Studies of this type are useful in suggesting what types of associations should be investigated more extensively in case control studies. The findings of most of these ecological studies have been summarized in several comprehensive review articles cited earlier and will not be reiterated at length here. For the sake of continuity, however, brief accounts of several of these studies are given below.

Page et al. (1976) and DeRouen and Diem (1977) examined the relationship between 20 year cancer mortality rates for parishes (counties) in Louisiana and the extent to which these parishes used Mississippi River water as a drinking water source. Although these two studies used the same data, their methods and interpretations of the data were quite different. Both studies found excess mortality for cancers of gastrointestinal organs in parishes using Mississippi River water.

A number of studies have been conducted using data from

Ohio and the Ohio River basin. Buncher (1975) performed a multiple regression analysis for Ohio River water and cancer mortality analogous to the Mississippi River water study of Page et al. Buncher found that drinking water from the Ohio River was not associated with cancer mortality rates higher than those associated with other drinking water sources in the counties studied.

Salg (1977) conducted extensive weighted and unweighted regression analyses of cancer mortality and water quality data from 346 counties of the Ohio River basin. The two water quality variables used were percent surface water usage (the percentage of a county's population receiving their public water supply from a river) and percent prechlorination (percentage of a county's population drinking prechlorinated[2] water). Only rectal cancer showed a consistent statistically significant elevation across race and sex groups (except for non-white females) for both water quality variables. Bladder cancer was significantly associated with both water quality variables for white males only.

Kuzma et al. (1977) studied cancer mortality in whites in the 88 counties of Ohio. Kuzma designated each county as a surface water county or a ground water county, depending on the drinking water source for the majority of people in the county, and compared average mortality rates for the two sets of counties using analysis of covariance. Harris et al. (1977) used the percentage of each county's population drinking surface water as one of the variables in multiple regression analyses. Both studies found stomach cancer (for males and females), bladder cancer (males only) and all

[2]Prechlorinated water is water to which chlorine has been added prior to filtration or other treatment to remove organics.

cancers combined (males only) to be significantly associated with surface water. Less agreement was observed at other sites.

Kruse (1977) examined the incidence of liver and kidney cancer among residents of Washington County, Maryland who had been enumerated in a private census of Washington County conducted in 1963 by the National Cancer Institute, John Hopkins School of Hygiene and Public Health, and the Washington County Health Department. Multiple regression analyses were conducted using the following nine variables: water supply (chlorinated, unchlorinated), sex, age, marital status, years of school, number of bathrooms in residence, cigarette smoking in 1963, number of years in 1963 residence, and church attendance. The relative risk for chlorinated versus unchlorinated water was defined to be the ratio of the adjusted incidence rates for the two groups. The risk ratio for cancer of the liver and bile ducts was 1.48 based on 47 cases and the risk ratio for kidney cancer was 0.96 based on 44 cases. Neither ratio was statistically significantly different from 1.0.

Cantor et al. (1977) performed weighted multiple regression studies relating site-specific cancer mortality data for whites by county in 923 urban U. S. counties to a number of explanatory variables (urbanization, educational level, population, 10-year percentage change in population, percentage of work force in manufacturing, and percentage of population grouped in 10 categories of foreign stock). The residual cancer mortality rates for those 76 counties with a majority of the population drinking from a supply sampled in the NORS or EPA Region V survey (EPA, 1975) were then compared to several measures of trihalogenated methanes. Urinary bladder cancer showed the strongest and most consistent association with THM exposure.

For the total sample of 76 counties in the study the correlation between bromine-containing trihalomethanes (BTHMs) and bladder cancer was strongly positive for both sexes ($r=0.21$, $p=0.06$ for females and $r=0.19$, $p=0.10$ for males). To evaluate for trends suggestive of a dose-response relationship, the counties in the study were grouped into three categories by percentage of the population drinking from water supplies sampled in the surveys mentioned above. The correlation coefficients between bladder cancer and BTHMs increased with increasing percentage of the population drinking from sampled supplies, reaching levels of $r=0.45$, $p=0.02$ for females and $r=0.38$, $p=0.06$ for males in the group where at least 85 percent of the population was on a sampled supply. Numerous additional analyses were conducted to evaluate the influences of possible confounding variables (such as high risk industries, social class, urban versus rural differences, and overall industrialization) and to check for other trends. The authors noted that their intent was to examine the consistency of the associations by analyzing the data in several different ways rather than emphasizing the statistical significance of individual findings in a study with multiple tests of statistical hypotheses.[3]

[3]Each of the studies discussed in this report includes numerous tests of statistical hypothesis. The probability of falsely significant associations is therefore high. For this reason it is difficult to interpret an individual statistically significant association selected from any one such study. The problem of how to interpret quoted levels of significance is compounded when comparing multiple studies based on different population sizes, using different statistical techniques, and testing different types and numbers of hypotheses. To measure the strength of the findings of such studies only in terms of levels of significance imparts a false sense of quantitativeness. We have chosen to discuss the findings of these studies in terms

Hogan et al. (1979) performed weighted and unweighted multiple regression analyses using site-specific cancer mortality data for whites by county and water chloroform contamination data from the NORS and EPA Region V (EPA, 1975) surveys. The results depended strongly on the type of weighting used in the analysis. Cancer sites showing the most consistent and strongest positive association with chloroform levels were the colon and rectum (combined) and the urinary bladder.

Carlo and Mettlin (1980) conducted an ecological study based on site-specific cancer incidence data by census tract in Erie County, New York for the years 1973 to 1976. Multiple regression analyses were performed using the above cancer data, directly measured total THM levels, and various social and economic parameters. The sites studied were the esophagus, stomach, colon, rectum, bladder and pancreas. For white males, pancreatic cancer was significantly correlated with total THM levels. No other significant associations were found. The authors state that this study lends little or no support to the hypothesis that THM levels which meet present standards are related to the incidence of human cancer.

Wilkins (1979) extended the preliminary study of Kruse (1977) into a two part ecological and case control cancer incidence study in Washington County, Maryland. The first part was an ecological study of liver, bladder, and kidney cancer incidence for the years 1963-1975 in about 30,000

[3](continued from last page) of the overall strength and consistency of positive associations rather than only by citing the levels of significance associated with individual findings. However, the concept of statistical significance is important, so we have included mention of statistical significance in places where such mention may aid in interpreting the results.

white male and female residents of Washington County over the age of 25. All of these subjects were included in the 1963 public health census of Washington County mentioned above in the discussion of the study by Kruse. Wilkins computed site and sex specific incidence rates adjusted for a comprehensive set of risk factors including age, smoking history, water source, years of residence in the same house, marital status, and socioeconomic status. Adjusted bladder cancer incidence rates for males and adjusted liver cancer incidence rates for females were somewhat higher in the group exposed to high levels of chloroform, but the differences were not statistically significant. Estimated relative risks were in the range 1.5 to 1.8 but the 95% confidence intervals for all relative risks included 1.0. This study included 33 liver cancer cases, 13 kidney cancer cases, and 28 bladder cancer cases.

The second part of the study was a case control study of liver cancer incidence in Hagerstown, Maryland. All cases and controls used Hagerstown municipal water, which comes from surface sources. Thirty six incident cases were matched to 72 controls by age, sex, and smoking history. Tap water samples were obtained from the homes of all 108 cases and controls, and were analyzed for chloroform. No significant difference was found in the chloroform content of tap water from cases and controls. The median chloroform content for cases was 105 micrograms per liter and for controls was 110 micrograms per liter.

An ecological study of cancer incidence in Iowa by Isacson et al. (1980) is currently nearing completion and will be mentioned here with the permission of Dr. Isacson even though results of the study are not yet available. This study uses cancer incidence data by municipality for the years 1969-1971 and 1973-1979. Over 100,000 incident cases

are included. Sites studied include bladder, breast, colon-rectal, kidney, lung-bronchus, pancreas, stomach, prostate, and multiple myeloma. Age-adjusted incidence rates for these sites are calculated by municipality. Municipal water sources are classified as surface, ground with well depth less than 150 feet, between 150 and 500 feet, or greater than 500 feet. The municipalities are stratified by population size into seven size ranges. Thus, age-adjusted incidence data are available for each combination of water source and municipality population size.

Contaminants under study include THMs, nitrates, heavy metals, and radioactivity. Water from wells greater than 500 feet deep has been found to contain measurable quantities of Radium 226. No appreciable radioactivity was found in water from shallow wells (<150 feet) or from surface sources. The preliminary report by Isacson et al. (1980) emphasized the importance of including well depth as a control variable because of differences in the types of contaminants typically present in water from shallow wells (<150 feet) and deep wells (>500 feet). As Cuello et al. (1976) have observed, water from shallow wells may contain higher levels of nitrate than does surface water in areas subject to agricultural runoff. Water from deep wells typically contains very little organic material and hence the THM level associated with a given chlorine dose would generally be lower in deep well water than in shallow well water.

Case Control Studies

Alavanja et al.

In 1978 Alavanja et al. (1978) published the first case control study associating chlorinated drinking water with gastrointestinal (GI) and urinary tract (UT) cancer. This

study is based on all GI and UT cancer deaths in seven upstate New York counties (Allegany, Cattaraugus, Chautuaqua, Erie, Rensselaer, St. Lawrence, and Schenectady) during 1968 through 1970. Gastrointestinal cancers were defined to be those of the esophagus, stomach, small intestine, large intestine, rectum, liver, intrahepatic bile ducts, gall bladder and bile ducts, pancreas, peritoneum, and retroperitoneal tissue. Urinary tract cancers were defined to be those of the kidney, pelvis of the kidney, ureter, and other unspecified urinary organs. The cases were obtained from computer tapes of New York state death certificates and were matched with an equal number of non-cancer deaths by age, race, sex, foreign versus U.S. born, county of usual residence and year of death.

Risk factors studied included chlorinated versus unchlorinated water, surface water versus ground water, urban versus rural, and occupation (high risk versus low risk). Urban areas were defined as communities of 2500 population or more and the densely settled fringe around cities of 50,000 or more. Water distribution maps were used to assign a water supply to the residence of each case and each control using the "usual place of residence" listed on the death certificates.

Risks were compared by computing odds ratios[4] and using

[4]Odds Ratio: One measure of the strength of association of, for instance, chlorinated water with rectal cancer is the risk of rectal cancer among those on chlorinated water divided by the risk of rectal cancer among those on unchlorinated water. This is called the relative risk. The odds ratio is an approximation to the relative risk and is one of the basic statistics used in analysis of data from case control studies. In the present example the odds ratio is defined to be the ratio of the odds of rectal cancer cases among those cases and controls on chlorinated water to the odds of rectal cancer cases among those cases and controls on unchlorinated water. In equation form this is the ratio

chi-square tests of significance. When potentially confounding variables were not controllable through matching, the cases and controls were stratified by the confounding variable and then analyzed by a chi-square technique. The analysis did not appear to stratify on the matching variables.

The authors gave the following statement as a summary of their conclusions,

> Males living in the chlorinated water areas of Erie, Rensselaer, and Schenectady counties and females living in the chlorinated water areas of Erie and Schenectady counties are at a greater risk of gastro-intestinal and urinary tract cancer mortality than are individuals living in unchlorinated water areas. Moreover this excess risk of GI and UT cancer mortality is not due to a disparity in the age, race, or ethnic distribution of the population or to an urban/rural factor, hazardous occupation, inorganic carcinogens (Cd, As, Be, Pb, Ni, NO_3) or a surface/ground water difference.
>
> Alavanja et al. (1978)

In site specific analyses, chlorinated water was shown to be significantly associated with excess cancer mortality of the esophagus, stomach, colon, rectum, liver and kidney, pancreas, and urinary bladder for both sexes combined and for males. For females, only stomach cancer mortality was

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[4](continued from last page) (a/c)/(b/d) = ad/bc where a and b are the numbers of rectal cancer cases on chlorinated and unchlorinated water respectively and c and d are the numbers of controls (deaths due to other causes) on chlorinated and unchlorinated water respectively. The chi-square test may be used to test for whether this ratio is significantly greater than (or less than) one. In applications one may subdivide (stratify) the population of cases and controls according to several categories, compute odds ratios for the individual categories, and also compute an overall "adjusted odds ratio". Techniques for doing this are well known (Mantel and Haenzel, 1959, page 736 and Gart, 1971, page 158).

significantly elevated.

The odds ratios reported by Alavanja et al. appear to be greatly influenced by the cases in one of the seven counties in the study, as noted by the NAS (1978) report. Erie County had 2177 of the 3446 cases in the study. The overall odds ratio for chlorination versus nonchlorination in Erie county was appreciably higher than the comparable ratio for all seven counties taken together (3.15 versus 1.79).[5] Alvanja et al. (1978) also found lung cancer mortality to be significantly elevated in urban areas supplied with chlorinated water as compared to urban areas supplied with unchlorinated water. (However, no such elevated risk was seen with chlorinated water in rural areas.) The authors considered the lung cancer association spurious and reasoned that it suggested the possible presence of confounding factors not accounted for in the study design. Kanarek and Young (1980) cautioned against making the a priori assumption that this association must necessarily be spurious. The lung has been shown to be involved in the metabolism and clearance of orally ingested chloroform (Fry et al., 1972) and therefore should not be summarily dismissed as a site where any associations found between chloroform and cancer must necessarily be spurious.

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[5]Kanarek and Young (1980) questioned the propriety of using a dichotomous chlorination/nonchlorination variable in this county since review of data in Alavanja's report to the EPA led Kanarek and Young to conclude that the vast majority of Erie County (98.5%) is supplied with chlorinated water. Further review of this report shows that the figure 98.5% is incorrect. About 9.9% of Erie County receive nonchlorinated water from private wells and about 1.3% receive nonchlorinated water from public supplies. Hence about 125,000 (11.2%) of the 1,113,000 people in Erie County receive unchlorinated water.

Brenniman, et al.

In an attempt to replicate the findings of Alvanja et al. (1978), Brenniman et al. (1980) conducted a case control study of GI and UT cancer mortality among whites in 70 Illinois communities using chlorinated or unchlorinated ground water. The authors confined their study to ground water because of potential confounding effects due to agricultural run-off and industrial sewage in surface water. All of Cook County, consisting mostly of Chicago, was also eliminated due to potential confounding. The study included 272 chlorinated communities and 270 nonchlorinated communities with similar urban/rural and similar SMSA[6]/non-SMSA characteristics. Cases and controls were taken from Illinois deaths for the period 1973-1976. Controls were selected (without matching) from a pool of non-cancer deaths after eliminating certain deaths (e.g., perinatal deaths).

Mantel-Haenszel stratified contingency table analyses were performed after stratifying by the following control variables: age (six age groups), sex, and residence (urban/rural and SMSA/nonSMSA). This technique permits computation and statistical analysis of odds ratios while controlling for the potentially confounding effects represented by the control variables.

Significantly elevated estimates of relative risk were found for colon and rectal cancer in both sexes combined and in females and for total GI tract (excluding liver) cancer in females. The authors considered these findings to be somewhat tenuous since the precision of the relative risks was not strengthened by stratification on several control variables. An additional puzzling finding was that of a slightly (but not significantly) lower incidence of total

[6]SMSA = Standard Metropoliton Statistical Area

gastrointestinal and urinary tract cancer in rural chlorinated communities than in rural nonchlorinated communities. In summary, the authors concluded that this study does not confirm the study of Alavanja et al. (1978) either in the strength or in the consistency of the associations.

Table II.2 gives a comparison of chlorination risk ratios for rectal cancer, colon cancer, and bladder cancer found by Brenniman et al. with similar ratios and their associated confidence intervals found in the case control studies of Struba, Gottlieb et al., Kanarek and Young, and Alavanja et al. The rectal cancer risk ratios of Brenniman et al. fall at the lower end of the 95% confidence interval of Struba and well within the 95% confidence intervals of Gottlieb et al. and Kanarek and Young. The 95% confidence intervals for all of these studies show considerable overlap. Although these comparisons ignore some differences in how these different risk ratios were defined and computed, they do indicate a degree of consistency among these studies in estimated rectal cancer chlorination risk ratios.

In making these comparisons it should be kept in mind that Brenniman et al. included only ground water. The other four case control studies included both surface water and ground water. Since ground water typically (but not invariably) contains less organics, the putative carcinogenic effect attributable to chlorination should be less, and hence odds ratios for chlorinated versus unchlorinated water should be less, than in a study where surface water was included. A direct comparison between Brenniman et al.'s results and those of Struba (1979) is possible, however, because Struba reported odds ratios for chlorinated versus unchlorinated ground water. These are 1.12, 1.33, and 1.57 for rectal, colon, and bladder cancer respectively. None of these is

significant at the p=0.05 level. The rectal cancer odds ratio lies within the 95% confidence limits for Brenniman et al.'s ratio shown in Table II.2. The odds ratios for colon and bladder cancer lie above Brenniman et al.'s upper 95% confidence limits. Confidence intervals for the above odds ratios of Struba are not available.

Kanarek and Young

Kanarek and Young (1980) examined the relationship between drinking water chlorination and cancer at a number of different sites in white Wisconsin females in a case control study based on death certificate data from the years 1972-1977. The sites investigated were the rectum, colon, stomach, esophagus, pancreas, liver, intrahepatic bile ducts, kidney, urinary bladder, lung, breast, and brain. Controls were matched one-to-one with 8029 cases on the basis of age, year of death, and county of residence. The analyses were conducted with logistic regression using urbanization (6 population size strata), marital status, and occupation as control variables. In this study, consisting only of females, less than 1% had high risk occupations and 63% were classified as "homemakers" on the basis of the occupation listed on the death certificate. To control for migration the study was limited to 28 Wisconsin counties with 20-year migration rates below 10%. Water chlorination exposure (as an indirect indicator of THM exposure) was represented by the average daily total chlorination dose (ppm) for each watersource for the 20 year period prior to the study. Pre- and post-chlorination dosages were represented separately in the same manner. The presence or absence of organics from rural runoff was also recorded for each source. These water source characteristics were obtained from questionaires sent to each water superintendent (97% final response rate).

Colon cancer was the only type of cancer for which a significant association with water chlorination was established. Odds ratios of 1.51, 1.53, and 1.53 were obtained for high, medium, and low average daily chlorine doses respectively, using the average daily chlorine doses for the 20 year period leading up to the study. These odds ratios were significant at the $p=0.02$ level.

For those exposed to rural runoff, odds ratios of 3.30, 3.60, and 2.74 were found for high, medium, and low average daily chlorine doses. These were significant at the $p=0.025$ level. For those not exposed to rural runoff, colon cancer mortality was not significantly related to chlorination ($p=0.13$). In the rural runoff analyses those cases and controls served by individual wells (13.5% of the colon cancer cases and controls) were excluded since the extent of contamination by organics other than THMs was unknown. The strong interaction between the presence of rural runoff and the increased risk associated with chlorination is consistent with the theory that THMs are formed through action of chlorine on humic substances from vegetative decay and rural runoff (Morris and Johnson, 1976).

Water purification (coagulation, sedimentation, and filtration) was examined as a potential THM modifier. When cases and controls were stratified by water purification (present/absent), urbanization, and marital status, odds ratios for colon cancer suggestive of a chlorination dose response relationship were found. These ratios, which were significant at the $p = 0.01$ level, were 1.70, 1.70, and 1.52 for the high, medium, and low chlorine dose categories. The corresponding 95% confidence intervals were (1.13, 2.53), (1.15, 2.53), and (1.10, 2.09). In the subsample exposed to rural runoff, stratification according to the above variables yielded colon cancer odds ratios of 3.27, 3.57, and 2.72 for

high, medium, and low chlorine dose categories. These were significant at the 0.004, 0.002, and 0.03 levels respectively. When well depth was added as a stratification variable (along with water purification, urbanization, and marital status) the above odds ratios were slightly increased to 3.43, 3.68, and 2.94. These were significant at the 0.003, 0.003, and 0.015 levels.

Odds ratios for rectal cancer were 1.39, 1.16, and 1.13 for high, medium, and low average chlorine doses. The corresponding confidence limits are shown in Table II.2. These odds ratios were not significant ($p = 0.40$ to 0.70). The 95% confidence interval on the odds ratio of 1.13 mentioned above was (0.61, 2.08), illustrating the large range of uncertainty associated with the small sample size (393 rectal cancer cases) in this study.

The major finding of this study is the significant association between female colon cancer mortality and exposure to chlorinated drinking water. This conclusion is strengthened by a number of special features of this study. Restriction of the study to only white females in counties with 20 year migration rates below 10%, use of average daily chlorine dose over the past 20 years as the primary exposure variable, examination of rural runoff, and controlling for water purification as a potential THM exposure modifier all serve to increase the sensitivity and specificity of the study and to eliminate many potential confounding factors.

Gottlieb et al.

Gottlieb et al. (1980a,b) conducted a case control study based on cancer mortality data from 20 south Louisiana parishes (counties) to examine the relationship between the Mississippi River as a source of drinking water and death from cancer of the rectum, colon, bladder, kidney, liver,

brain, pancreas, and prostate. To reduce the likelihood of confounding due to urban lifestyle factors, parishes were grouped according to industrial and urban characteristics and cases were matched to controls within each parish group by age, race, and sex, after eliminating deaths due to potentially confounding cases. Other control variables included occupation, proximity to industrial sites, and Acadian ancestry.

Water exposure variables included surface (Mississippi River)/ground, chlorinated/unchlorinated, total chlorine content, and total organic content. All of these were based on the residence listed on the death certificate. In addition, a measure of the time spent on surface water was developed by grouping cases and controls into the categories: "mostly surface" - people who were born and died in a surface water parish; "some surface" - people who either were born or died in a surface water parish; "possible surface" - people who died on a ground water source but who had an unknown or out-of-state birth place; and "least surface" - those who were born and who died on ground water. This variable is called the "sourcelife" variable. In addition to examining water quality associations, time-space clustering analyses, and correlations with occupation and proximity of residence to industrial sites were performed for each of the eight cancer sites.

A major finding of the study was that rectal cancer was strongly associated with Mississippi River (surface) water. Rectal cancer odds ratios showed an increasing trend with increasing estimated exposure to surface water. The odds ratio for those who were born and died on surface water to those who were born and died on ground water was 2.07 with a 95% confidence interval of (1.49, 2.88). Among those on Mississippi River water, the risk increased with increasing

proximity to the mouth of the river.

For those in the study population whose water source 10 years prior to death was known, the rectal cancer odds ratio for surface water to ground water was greater than 1.0 for each of the four race-sex classifications. The increase was statistically significant for three of the four groupings and was not statistically significant for white females. For those whose water source was unknown 10 years prior to death, the rectal cancer odds ratio was not statistically different from one in any of the four race-sex classifications. No time-space clustering of cases or controls were observed and there was no association with Acadian ancestry. Although one occupational group (construction workers) had an odds ratio significantly elevated at the 5% level, the number of cases involved (44) was considered not likely to have a confounding effect on overall results. Formal examination of the data for occupational confounding using multiple linear regression was not conducted.

In contrast to the association of rectal cancer with surface water, no significant association was observed for colon cancer, in spite of the fact that the number of colon cancer cases in the study (1167) was greater than the number of cases at any other site. The author suggests that the association between colon cancer and water source found in earlier ecological mortality (not case control) studies of Mississippi River water and cancer (e.g., DeRouen and Diem, 1977) may have been due to confounding with urban lifestyle factors. No consistent water quality association was noted with the other sites in the study, including the liver and the kidney.

The lack of association of bladder cancer with water quality is inconsistent with ecological studies of Harris et al. (1977), Cantor et al. (1977), Hogan et al. (1979), Salg

(1977), Kuzma et al. (1977), DeRouen and Diem (1977) and Page et al. (1976) and with case control studies of Alavanja et at. (1978) and Struba (1979). Examination of the bladder cancer analyses showed some (non-significant) trends which suggested to the authors the confounding of surface water with some other factors which are not yet known. For example, there is a consistent but non-significant increased bladder cancer risk for black and white females on ground water with years on source known. This could be spurious or it could indicate the presence of contaminants associated with industrial or related runoff. For females with years on source unknown there is a non-significant increased bladder cancer odds ratio associated with surface water. A survey of next-of-kin to estimate length of residence for a sample of those with years on source unknown showed no difference in their lengths of residence from those with known lengths of residence.

Brain cancer showed a slight but non-significant increased risk with chlorinated ground water. It is biologically plausible that the brain could be a site affected by chloroform because the anesthetic chloroform enters the brain and chronic chloroform ingestions have been associated with pathological changes in central nervous system tissue detectable at autopsy (NIOSH, 1974, Polkina, 1965, Challen et al., 1958, Heilbrunn, 1945, and Oettingen, 1964). Since almost all the chlorinated water in the study area is located near chemical, plastic, and petroleum industries, the brain cancer effect could be due to confounding. On the other hand, the recent discovery of high levels of ground water contamination by synthetic organics suggests that the possibility of well-water contamination by some specific types of industrial pollutants merits further investigation.

Pancreatic cancer showed a borderline association with chlorinated water but results of stratified analyses did not reveal a clear pattern of increased risk. Prostate cancer showed an association with surface water only for those dying before 1969. However the lack of correlation with the "sourcelife" variable (representing a measure of time on surface water) suggests that this association is probably due to confounding. Among those on ground water, unchlorinated water seemed to be associated with increased risk. The authors noted that most of the unchlorinated ground water supplies are individual or small-town wells accessing different aquifers. Hence a consistent risk pattern seems unlikely to be due to these individual wells. (However these may be shallow wells contaminated with industrial pollution.)

A continuation of this study has recently been completed which examines nine additional cancer types: esophagus, stomach, lymphoma (Hodgkins and non-Hodgkins), multiple myeloma, leukemia, lung, breast, and malignant melanoma. The results of this study are not yet available.

Struba

Struba (1979) conducted a case control study based on mortality data from people who died within North Carolina at an age of greater than 45 years during the four year period 1975-1978. The three cancer sites studied were the rectum, colon, and urinary bladder. For each site, between 700 and 1500 cases were matched with controls by age, race, (white/nonwhite), sex, and one of three geo-economic regions of the state (Coastal, Piedmont, Mountain) after excluding non-cancer deaths where the death certificate listed a cancer as contributary or underlying cause of death. For colon and rectal cancer the following precancerous colonic disorders

were also excluded: ulcerative colitis, familial polyposis, and adenomatous polyposis. The minimum sample size of 700 was selected as being capable of detecting true odds ratios somewhat less than 1.5 at the p=0.05 level (two-tailed) with a power of 0.10, based upon (1) the sample size estimation procedure of Schlesselman (1974) for case control studies, (2) information from previous ecological studies and (3) the results of Alavanja et al.

The water data were classified by source, treatment, and previous use as follows: source (ground, surface uncontaminated and surface contaminated by upstream pollution); treatment (none, prechlorinated, postchlorinated and both pre- and postchlorinated); and previous use (for contaminated surface water only, one of 15 categories of upstream pollution). Using these water classifications, three different types of analyses were conducted, each determined by one type of exposure. The three types were: (1) surface/ground and chlorinated/unchlorinated dichotomous analyses; (2) exposure "gradients" based on combinations of source and treatment representing what was assumed to be a gradient of increasing carcinogenic potential (ground unchlorinated, ground chlorinated, surface chlorinated uncontaminated, etc.) and computing odds ratios relative to the ground uncontaminated category; and (3) an examination of types of upstream discharges for surface water contaminated by "previous use." Both multivariate techniques and stratified contingency table analyses were used for comparison, and to control for possible residual confounding by variables such as age and socioeconomic status. The variables used for stratification were the matching variables - sex, race (white/nonwhite), age (45-65, over 65) and region (Coastal, Piedmont, Mountain) - and two other variables - urbanization (urban/rural) and socioeconomic status based on occupation

(undefined, prcfessional, clerical, skilled, unskilled, and homemakers).

For rural areas Struba consistently found odds ratios which were small (1.3 to 2.0) but significant for each of the three cancer sites and each of the two dichotomous water quality variables in many stratified or combined analyses. Odds ratios for urban areas (population above 10,000) were generally not significant. These analyses also showed urbanization to be an effect modifier for colon cancer and a likely confounder for rectal and bladder cancers.[7] Socio-economic status was identified as a likely confounder for rectal and bladder cancers. Occupation was investigated as a possible confounder for bladder cancer but multivariate analyses showed no evidence that it was acting as such in this study.

Odds ratios for females were slightly but consistently higher than those for males in the stratified analyses, especially for colon cancer. For colon and rectal cancer, but not for bladder cancer, odds ratios were higher for the older age group (above 65) than for the younger age group (ages 45-65). Racial differences in odds ratios were generally small and showed no trend. Odds ratios for

[7]To say that urbanization is an effect modifier for the association of chlorination with colon cancer means that association differs in strength between urban and rural areas, (i.e., the odds ratio for rural areas differs from that for urban areas). In other words, urbanization modifies whatever effect chlorination seems to be having on colon cancer. That urbanization is a confounder for the association of chlorination with rectal cancer means that the crude odds ratio computed by combining urban and rural data differs from an "adjusted odds ratio" computed as a weighted average of odds ratios for urban and rural areas taken separately. This could occur if urbanization itself affected rectal cancer risk and was correlated with water chlorination. Confounding and effect modification are two different concepts. A given variable may act as one, both, or neither

treatment were slightly larger than odds ratios for source (e.g., 1.41 versus 1.38 for all sites combined).

To provide some estimate of migration effects, cases and controls were stratified by place of birth and death (born and died in the same county, born and died in North Carolina, and died in North Carolina with place of birth unrestricted) and then substratified by region, age, race, sex, and urbanization. Odds ratios for treatment (chlorinated/unchlorinated) were computed for all the strata. The three categories defined by place of birth and death were considered to represent increasing likelihood of migration and it was expected that decreasing odds ratios with increasing migration should be seen if water treatment is related to cancer mortality. For all three cancer sites combined, and for each site taken separately, the group with birth and death in the same county had the highest odds ratio. For colon and bladder cancer, but not for rectal cancer, the groups with no restriction on birthplace (most migration) had the lowest risk ratios.

To provide an indication of the validity of using ground water as a comparison category and to assess the effects of well depth, Struba stratified by region (Coastal, Piedmont, Mountain) because well depth increases in North Carolina from the coast (<50 feet) to the mountains (>400 feet). With some exceptions odds ratios typically increased from the coast to the mountains, with ratios in the Piedmont being generally intermediate.

Struba interpreted this result as being consistent with a stronger contrast between surface water and water from deep wells than between surface water and water from shallow

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[7](continued from last page) of these. Kleinbaum et al. (1979) contains a detailed discussion of these concepts.

wells, which are known to be susceptible to contamination by surface water seepage into ground water aquifers. This result is consistent with findings being obtained by Isacson, et al. (1980) as discussed in the section on ecological studies. However, Struba noted that the effect could have other explanations such as differences in water treatment practices or confounding by uncontrolled factors such as dietary habits and other aspects of life style.

Conclusions

The case control studies discussed in this section have considerably sharpened the evidence for elevated risks associated with water quality provided by earlier ecological studies reviewed by the National Academy of Sciences (1978, 1980). Table II.1 summarizes the descriptive features of these studies and Table II.2 presents a summary of some of the risk ratios from these five case control studies. As can be seen from Table II.2, rectal cancer odds ratios show a rather consistent elevation in all the studies, including the studies of Kanarek and Young (1980) and Brenniman et al. (1980) where these ratios were not statistically significant. It must be recognized that these odds ratios are small by traditional epidemiological standards and could be produced by a moderate degree of confounding which could go undetected.

For colon cancer the results are much less clear. Gottlieb et al. (1980a,b) conducted an extensive study including 1167 colon cancer cases and found essentially no difference in colon cancer risk between Mississippi river water and ground water. Both Struba (1979) and Kanarek and Young (1980) found elevated odds ratios for colon cancer, with the odds ratios of Kanarek and Young being somewhat higher than those of Struba. Likewise, the five studies do

not present a consistent picture for bladder cancer. Detailed examination of data in the study by Gottlieb et al. suggests that some unknown confounding factors may be influencing the results. There is a case control interview study now being conducted by Cantor et al. which should help resolve the present uncertainty regarding bladder cancer risks. As outlined in Cantor et al. (1980), this study will be based on interview data from over 3000 cases of bladder cancer newly diagnosed in 1978 and over 6000 controls. Use of interview data should permit controlling for numerous lifestyle and exposure variables which cannot be taken into account in the present generation of case control studies, which are all based on death certificate data. This study is also much larger than those completed thus far and consequently is expected to contribute significantly to the evidence regarding bladder cancer. A case control study of colorectal cancer is also being conducted by Shy and Struba and which is based on interview data from about 450 incident cases and about 900 controls.

Liver cancer mortality was investigated in five case control studies, only one of which (Alavanja et al., 1978) found a statistically significant elevation in risk with chlorinated water. Specifically, Alavanja et al. found an odds ratio of 2.19 ($p<0.005$) for liver and kidney cancer combined in both sexes combined. Gottlieb (1980) reported a non-significant odds ratio of 0.90 with a 95% confidence of (0.67, 1.19) for liver cancer based on 541 cases; Kanarek and Young (1980) found a non-significant odds ratio of 1.09 (0.51, 2.34) for his "high chlorine" group as compared to the group with no chlorination; and Brenniman et al. reported an odds ratio of 1.00 (no confidence interval stated) based on 57 cases. The liver cancer case control study by Wilkins (1979) examined measured chloroform content in the drinking

TABLE II.1

CASE CONTROL STUDIES

	ALAVANJA et al. (1978)	BRENNIMAN et al. (1980)	KANAREK & YOUNG (1980)	GOTTLIEB et al. (1980a,b)	STRUBA (1979)
RACE	All	White	White	White/Black	White/Non-white
SEX	Male/Female	Male/Female	Female	Male/Female	Male/Female
POPULATION	7 upstate New York counties; 1968-70 deaths	70 Illinois counties; 1973 -76 deaths	Wisconsin; 1972-77 deaths	20 south Louisiana parishes	N. Carolina; 1975-78 deaths over age 45
WATER VARIABLES	Chlor./unchlor.; Surface/ground	Ground water only:chlorinated/unchlorinated	Ave. water chlor. dose of 20 years ago; Ave. pre-postchlor. doses; Exposure to rural runoff	Surface (Miss. River/ground); chlor./unchlor.; Surrogate for time on surface water; Total chlorine; Total organics	Source (s/g, w/ without contamination); Treatment (none, prepostchlor., both); Previous use
MATCHING VARIABLES	Age; race; sex; for. vs. U.S. born; yr. of death; county of residence	None (case to control ratio = 1:14)[a]	Age; year of death; county of residence	Age; sex; race; parish group; some confounding deaths omitted	Age; sex; race; 3 geoeconomic regions[b]

TABLE II.1
(continued)

	ALAVANJA et al. (1978)	BRENNIMAN et al. (1980)	KANAREK & YOUNG (1980)	GOTTLIEB et al. (1980a,b)	STRUBA (1979)
OTHER VARIABLES EXAMINED	Urban/rural; occupation	Age; sex; urban/rural; SMSA/nonSMSA	Urbanization; occupation (<1% were high risk); marital status	Occupation; proximity to industrial site; Acadian ancestry	Occupation; urbanization; Socioeconomic status
MOBILITY CONTROLS	Study counties are stated to have low rate of migration	_____	Study limited to 28 Wisconsin counties with 20-year migration rates below 10%	Cases and controls divided into 4 categories by length of time on surface water	Sep. analysis for categories: born & died in same county; born & died in N.C.; died in N.C.
OTHER SPECIAL FEATURES OF THE STUDY[c]	(+) Lung cancer risk found in urban chlorinated areas	_____	Rural runoff & dose-response effects observed	Time-space-clustering; numerous other substudies	Analyses for confounding & effect modification, migration, exposure-response gradients

TABLE II.1
(continued)

	ALAVANJA et al. (1978)	BRENNIMAN et al. (1980)	KANAREK & YOUNG (1980)	GOTTLIEB et al. (1980a,b)	STRUBA (1979)
SITES INVESTIGATED AND SAMPLE SIZES[a]	Site specific for gastrointestinal (GI) & urinary tract (UT) cancers	Site specific for GI & UT cancers	Site specific for GI, UT, brain, lung, breast	Rectum, colon urinary bladder, kidney, liver, brain, pancreas, prostate	Rectum, colon, urinary bladder
PRINCIPAL RESULTS[c]	(+) for GI & UT cancer for chlor./unchlor. in urban males and females	(+) for colon & rectum in F and in M & F combined; (+) for total GI tract (excluding liver) in F; (NS) for other sites.	(+) for colon with chlor.; (NS) for colon cancer with chlor. in population not exposed to rural runoff; dose effect for chlor. when rural runoff and water purification are accounted for.	(+) for rectum; increasing risk ratios with increasing time on surface water & increasing proximity to mouth of Miss. (NS) for other sites.	(+) chlor./unchlor. & surface/ground for each of three sites in rural (but not urban) areas; Bladder cancer typically showed largest odds ratios followed by rectum and then colon.

For footnotes see next page.

Footnotes for Table II.1

[a]Some 43,666 controls were used at each site by Brenniman et al. (1980). Deaths excluded as controls were: congenital anomalies, perinatal causes, pregnancy complications, infectious diseases, mental disorders, senility.

[b]Death certificates listing any cancer as a contributing cause were excluded from the controls by Struba (1979). For colon and rectal cancer death certificates indicating the presence of ulcerative colitis, familial polyposis coli, and adenomatous polyposis were also excluded from controls. Cases were excluded when it was not clear from available information whether the cancer at the site of interest was primary or metastatic.

[c]The designation (+) indicates that the odds ratios were significantly greater than one at the level $p<0.05$.

[d]Sample sizes for rectal, colon, and bladder cancer in these studies are as follows: Alavanja et al.: (obtained from Alavanja et al., 1977) rectal - 393, colon - 1064, bladder - 295 (the controls were matched one to one with the cases); Brenniman et al.: rectal - 295, colon - 1237, bladder - 284 (the same 43,666 controls were used for each site); Kanarek and Young: rectal - 393, colon - 1601, bladder - 230 (the controls were matched one to one with the cases); Gottlieb et al.: rectal - 692, colon - 1167, bladder - 759 (the controls were matched one to one with the cases); Struba: rectal - 702 (687 controls), colon - 1484, (1660 controls), bladder - 802 (801 controls).

TABLE II.2

CANCER RISK ODDS RATIOS AND 95% CONFIDENCE INTERVALS
(CLORINATED VERSUS UNCHLORINATED)

SITE	ALAVANJA et al. (1978)[c]	BRENNIMAN et al. (1980)[d]	KANAREK & YOUNG (1980)[b]	GOTTLIEB et al. (1980a,b)[a,e]	STRUBA (1979)[a,e]
Rectum	1.93 (1.32, 2.83)	1.26 crude (0.98, 1.61) 1.22 adjusted	1.39 high (0.67, 2.86) 1.16 medium (0.58, 2.32) 1.13 low (0.61, 2.08)	1.41 (1.07, 1.87)	1.53 (1.24,1.89)
Colon	1.61 (1.28, 2.03)	1.08 crude (0.96, 1.22) 1.11 adjusted	1.51 high (1.06, 2.14) 1.53 medium (1.08, 2.00) 1.53 low (1.11, 2.11)	1.05 (0.95, 1.18)	1.30 (1.13,1.50)
Bladder	1.69 (1.11, 2.56)	1.04 crude (0.81, 1.33) 0.98 adjusted	1.04 high (0.43, 2.50) 1.03 medium (0.42, 2.54) 1.06 low (0.60, 3.09)	1.07 (0.84, 1.36)	1.54 (1.26,1.88)

See next page for footnotes.

Footnotes for Table II.2

[a]Calculated for both sexes and all races combined.

[b]Calculated for white females and for high, medium and low average daily chlorine doses compared to no chlorination. Odds ratios and confidence intervals computed by logistic regression, controlling for urbanization, marital status and site-specific occupation.

[c]Calculated for both sexes and all races combined. Confidence intervals were not stated in Alavanja et al. (1978). We calculated them by applying the method in Fleiss (1979) to data in Alavanja et al. (1977).

[d]Calculated for Caucasians of both sexes. Adjusted values were adjusted for age, sex, urban/rural, and SMSA/nonSMSA. Confidence intervals were not stated in original report. We calculated them by applying formulas in Fleiss (1979) to data on total cases and total controls in Table II.3.

[e]Struba and Gottlieb et al. also computed odds ratios for surface water versus ground water. These ratios are different from the ratios shown in Table II.2 and are listed here for comparison. The ratios and confidence intervals obtained by Struba are as follows: rectum 1.55 (1.26, 1.91); colon 1.27 (1.10, 1.46); bladder 1.48 (1.22, 1.80). Those obtained by Gottlieb et al. are: rectum 1.51 (1.21, 1.90); colon 0.95 (0.88, 1.03); bladder 1.08 (0.87, 1.33).

TABLE II.3

DATA FROM THE CASE CONTROL STUDY OF BRENNIMAN et al. (1980)[a]

I. CASES

	Rectum		Colon		Urinary Bladder	
	C[b]	UC[b]	C	UC	C	UC
Total Cases	194	101	771	466	174	110
SMSA	116	40	426	142	96	34
Non-SMSA Urban	35	33	192	153	38	37
Non-SMSA Rural	43	28	153	171	40	39

II. CONTROLS

	Chlorinated	Unchlorinated
Total Controls	26,372	17,294
SMSA	14,063	5,635
Non-SMSA Urban	5,829	5,621
Non-SMSA Rural	6,480	6,038

[a]These data are from the study by Brenniman et al. (1980). They were not included in the preprint of the study available to us and were kindly furnished by Dr. Brenniman (personal communication). The cases and controls are divided into those within a standard metropolitan statistical area (SMSA) and those not within a SMSA. The non-SMSA cases and controls are further divided into urban and rural. The same controls were used for comparison with cases at each of the three cancer sites.

[b]C = chlorinated, UC = unchlorinated

water of 36 liver cancer cases and 72 controls and found no statistically significant difference in chloroform concentrations.

Evidence for Causality

The epidemiological studies reviewed provide extensive human data linking indirect measures of water quality to increased gastrointestinal and urinary tract cancer. The central issue addressed by these studies is whether synthetic organics in drinking water cause cancer in humans at the levels present in drinking water. While there is probably agreement that the accumulated scientific evidence is still not sufficient to make this inference of causality, there is increasing epidemiological evidence to suggest the likelihood of a causal relationship for rectal cancer and to a lesser extent for colon and urinary bladder cancer. The recent case control studies reviewed here tend to confirm the associations of bladder, rectal and colon cancer with water quality which were suggested in the earlier ecological studies reveiwed by the National Academy of Sciences (NAS, 1978 and 1980).

For the purpose of considering what type of additional studies are needed, it is instructive to review what aspects of epidemiological associations should be considered before one is justified in deciding that their most likely interpretation is casuation. This problem was discussed by Sir Bradford Hill (1965) who gave a conceptual framework in the form of nine criteria to be considered when deciding whether scientific evidence from epidemiological and other studies is sufficient to support the inference of causation. His criteria are: (1) strength of association; (2) consistency of association by different persons, in different places, circumstances and times; (3) specificity, including

the relative absence of spurious associations; (4) temporality (cause must precede effect); (5) dose-response gradient (increasing effect with increasing dose); (5) biological plausibility; (7) coherence (agreement with known facts about the natural history of the disease); (8) experimental evidence; and (9) analogy with previous situations in which causality was established. We will discuss the studies completed to date in terms of several of these criteria and will indicate what additional types of information need to be obtained.

Strength of association

The case control studies completed to date have found rectal, bladder, and colon cancer risks associated with chlorinated water to be a factor of about 1.1 to 2.0 higher than for unchlorinated water. Risk ratios for surface water versus ground water (much of which is unchlorinated) are similar. These risk ratios are large enough to be of concern but yet small enough to be difficult to separate from confounding risks associated with other environmental factors such as smoking, diet, air pollution, occupation, and "urban lifestyle."

By traditional epidemiological standards risk ratios below about 2.0 (which include nearly all of the risk ratios discussed in this report) are generally subject to doubt no matter how large the study. Such ratios can be largely or entirely due to a moderate degree of confounding which would be difficult to detect even in large studies. For example, equation (1) of Schlesselman (1978) implies that a confounding variable with a risk ratio of 4 and with prevalences in the exposed and unexposed groups of 0.30 and 0.10 respectively could produce an apparent risk ratio of 1.46 when the true risk ratio was 1.00. Thus all of the

apparent increase in cancer risk associated with chlorinated water in these studies could be explained by confounding by variables (such as smoking) which could not be taken into account within the limitations of present study designs and methodology.

All of the case control studies discussed in this report are based on cancer mortality rather than incidence and use data from death certificates rather than from more complete information sources such as interviews. Death certificates contain very little information with which to evaluate potentially confounding factors. Dietary, smoking, drug, migration, and lifetime occupational histories are not available.

All of the case control studies have used the residence on the death certificate as a basis for estimating exposure. If some cancer patients moved to new residences near major medical centers after diagnosis, and if the water sources associated with the new residences were more likely to be chlorinated than those associated with the previous residences, then a spurious association between cancer risk and chlorinated water could result. A related possible source of bias is that due to any differences in rates of survival for cancer patients on chlorinated water, because of possible proximity to better medical facilities, higher socioeconomic status, or other factors.

In addition to the methodological limitations of present studies that could result in overestimation of true risk ratios, there are a number which should result in underestimation of risk ratios. Examples of these are: (a) failure to control for migration prior to disease diagnosis, (b) misclassification of the cause of death on death certificates and (c) use of chlorination as a substitute for direct measures of concentrations of organic contaminants.

Polissor (1980) showed that underestimation of migration during the latency period but prior to diagnosis of the disease would yield underestimates of relative risk whenever the true relative risk was above 1.0. This is because the observed "exposed" group contains some people who only recently migrated into the group and whose underlying risk of disease is more similar to those in the unexposed group. Similarly, the observed "unexposed" group contains some people whose true risk is nearer to that of those in the exposed group. Hence the observed risk ratio will be somewhat less than the true risk ratio whenever the true risk ratio is greater than 1.0. It can also be seen that the extent of this underestimation will be greater for diseases with longer latency periods.

Engel et al. (1980) estimated that malignant neoplasms were underreported by 10% on death certificates and vascular diseases were overestimated by 10%. This would produce an underestimate of cancer risk ratios.

Use of chlorination as a surrogate for total organics may yield underestimates of relative risks, especially if some of the chlorinated sources (e.g., deep wells) contain very little organic contaminants. Among the highest risk ratios seen in the recent studies were those found by Kanarek and Young (1980) for chlorination effect on colon cancer in the subsample exposed to rural runoff. These ratios were 3.27, 3.57, and 2.02 for high, medium and low chlorine doses respectively. Comparable odds ratios for the overall sample were 1.51, 1.53, and 1.53.

The above discussion of methodological problems associated with the case control studies completed to date is by no means exhaustive. An enlightening general review of subtle and not so subtle biases which may influence the outcome of epidemiological research is given by Sackett (1979).

Consistency

Rectal cancer mortality has been consistently associated with water quality in a number of different studies. The case control studies of Struba, Gottlieb et al., and Alavanja et al. and the ecological mortality studies of Salg and Hogan et al. found this association. The case control studies of Kanarek and Young and Brenniman et al. did not find a statistically significant increase in rectal cancer, although point estimates of risk ratios from these studies fell at the lower end of the confidence intervals for the other studies, as shown in Table II.2.

Bladder cancer mortality increases were found in case control studies by Struba and Alavanja et al. and in ecological mortality studies by Salg, Hogan et al., Cantor et al., Page et al., DeRouen and Diem, Kuzma et al, and Harris et al. Case control studies by Gottlieb et al., Kanarek and Young and Brenniman et al. did not find significant increases. The risk ratios found in these three studies were in the range 0.98 to 1.07.

Colon cancer mortality was found to be associated with water quality in case control studies by Struba, Kanarek and Young, Alavanja et al. and (in certain cases) by Brenniman et al. Gottlieb et al. found no association of colon cancer mortality with Mississippi River water (as compared to ground water) in a case control study involving 1167 colon cancer cases. The risk ratio in Gottlieb's study was 0.95 with a 95% confidence interval of 0.88 to 1.03. Cancers at other sites have not shown a consistent pattern of association with water quality variables in studies conducted to date.

Specificity

Hill observed that evidence for causality is strengthened when the putative cause may be associated with one

specific effect. However, he also cautioned that the lack of specificity should not be taken to imply lack of causality, since one cause may produce multiple effects. In a forthcoming publication Rothman (1981) discusses Hill's criteria and concludes that the specificity criteria should not be used to judge causality. In the case of drinking water some lack of specificity should not be surprising because several organs are likely to be involved in the metabolism, storage, and clearance of the many different contaminants present in water.

Alavanja et al. (1978) found increased lung cancer in urban users of chlorinated water and regarded this as a spurious association, suggesting the possible presence of a confounding factor that had not been taken into account in the study design. Brain cancer and breast cancer associations have also been considered as possibly spurious. While none of these three cancer sites has shown any consistent association with drinking water quality, experimental studies of chloroform metabolism quoted in Kanarek and Young (1980) have yielded results which should caution against assuming that such associations are necessarily spurious.

Orally ingested chloroform is primarily excreted by the lung in humans and seems to be excreted much more slowly and biotransformed by adipose tissue to a greater extent in subjects with greater amounts of adipose tissue (Fry et al., 1972). In addition, the lung has been shown to be one of the organs involved in the metabolism and transformation of toxic compounds (Weisburger and Williams, 1975). Males excrete chloroform more rapidly than females and thin people more rapidly than fat people. These results, together with the well-known fat solubility of chloroform, also suggest that chloroform may be taken up and metabolised by the adipose

tissue in the breast. (However, since most of the chloroform is excreted, a build-up in breast tissue or in breast milk similar to that seen with DDT and PCBs would not be expected.) That chloroform or its metabolites may be taken up by the brain is suggested by the central nervous system symptoms seen in acute and chronic chloroform ingestions reported in the literature (Challen et al., 1958 and Heilbrunn et al., 1945), and by its chemical composition as a small fat-soluble molecule. Such a molecule would be expected to be capable of crossing the blood-brain barrier. Thus there is evidence to suggest that organs such as the lung, brain, and breast may be involved in the metabolism of chloroform and thus are potential sites for chloroform-induced cancer.

Temporality

Cause must precede effect. Because of the latency period for gastrointestinal and urinary tract cancer, the environmental exposure factors which should be investigated are those between 10 and 30 years prior to diagnosis. Present studies use current levels of exposure as indirect measures of past exposure.

Dose-response gradient

Case control studies of Gottlieb et al., Struba, and Kanarek and Young have all investigated dose-response effects by attempting to determine whether there are increasing risk ratios with increasing exposure to organics in drinking water. No clear trend has been established. Gottlieb et al. showed increasing rectal cancer mortality rates with increasing exposure to surface water. This suggests a dose-response gradient for rectal cancer. Kanarek and Young showed results suggestive of a colon cancer dose-response

gradient when effects of water purification and rural-runoff were taken into account.

One difficulty related to the demonstration of dose-response effects has been the extreme variability in levels of measured organics in the same water source. Hogan et al. (1979) noted individual variations ranging from -77.8% to +182.2% when chlorofrom levels were measured in drinking water supplies of 12 cities on two occasions several months apart. McKinney et al. (1976) reported marked variations in monthly average chloroform contents at a single location during a year. The effect of this large temporal variation in chloroform content is magnified by the 10 to 30 year latency period between the initiation of precancerous changes and the diagnosis of cancer. Cancers developing now should be correlated with water quality of 10 to 30 years ago. Water quality parameters for this period are usually not accurately known and can only be crudely estimated. In view of the large month-to-month variation in chloroform content, the possibility of accurately estimating trihalogenated methane levels of 10 to 30 years ago seems quite remote.

A more basic difficulty in attempting to detect dose-response gradients lies in obtaining quantifiable direct measures of exposure. The volatile organics, including the trihalogenated methanes, comprise only about 10% of the total organics in drinking water (NAS, 1977). Chlorination dose, or even trihalogenated methane content, may not be a reliable indicator of the carcinogenic potential of all the organic material in drinking water.

As Isacson et al. (1980) have observed, water from deep wells (>500 feet) contains very little organic material and hence the amount of halogenated organics formed by the addition of a given amount of chlorine to water from a deep well would be expected to be much less than would be formed

by the addition of the same amount to water from a shallow well. Not controlling for well depth while using chlorine dose as the exposure variable could decrease the ability to establish a dose response gradient.

In the absence of reliable exposure data it is not surprising that dose response effects have not been consistently detected thus far. Hence the current absence of consistent dose-response relationships should not be taken as strong evidence against causality. Epidemiological studies using case interview data and directly measured exposure levels would permit a much more thorough investigation of dose response effects. Case interview studies can produce the information needed to control for other environmental exposures (e.g., smoking, alcohol, diet, coffee, drugs (prescription and otherwise), occupational exposure, and for predisposing medical, ethnic, and socioeconomic conditions).

Coherence (agreement with existing knowledge)

Coherence means that a cause-and-effect interpretation of the data should not seriously conflict with existing knowledge about the biology and natural history of the disease. The fact that the cancer sites showing the strongest and most consistent association with drinking water quality in human studies (rectum, colon, and urinary bladder) are different from those affected by chloroform in rats (kidney) and mice (liver) does not of itself imply lack of causality. Species-to-species differences and differences between the sexes within a species are commonly seen in animal studies of cancer and are attributed largely to metabolic and hormonal differences. Much of the discussion about whether low level exposure to substances which are known to be carcinogens at high doses can result in measurable amounts of cancer has to do with the extent to

which detoxification mechanisms can remove low levels of chemicals before they can initiate a cancer. This subject is discussed in chapter III.

Experimental evidence

This criterion refers to the relationship between epidemiological findings and results of laboratory experiments involving animals, natural (unplanned) "experiments" such as occupational exposures or accidental ingestions involving humans, and basic theoretical and experimental work to understand mechanisms of carcinogenesis. The National Academy of Sciences Safe Drinking Water Committee (NAS, 1977) called attention to the similarity between cancer in humans and cancer in animals and concluded that chemicals carcinogenic to animals are likely to be carcinogenic to man, and vice versa.

In addition to the animal assays of carcinogenicity, a number of recent studies have shown that concentrates of non-volatile organics in drinking water are mutagenic in bacterial and mammalian cells and can induce cellular transformation in human and mouse fibroblasts. In particular, Loper et al. (1978) found city-specific patterns of dose-dependent bacterial mutagenicity for non-volatile organic concentrates prepared from drinking water by reverse osmosis concentration followed by organic extraction. One sample, prepared from New Orleans drinking water, was shown to transform mouse fibroblasts, yielding cells which exhibited some properties of tumor cells. Gruener and Lockwood (1979) took recycled water from a treatment plant and concentrated it 1000 times by reverse osmosis to achieve a total organic content of 700 micrograms per milliliter (approximately 71 times the nonvolatile total organic content of 9.8 miligrams per liter reported in the NORS for Miami

drinking water (EPA, 1975). This concentrate was not mutagenic for bacterial cells but was mutagenic for mammalian cells and induced cellular transformation in human embryonic lung fibroblasts. Cheh et al. (1980) formed concentrates of water produced in a laboratory simulation of a drinking water treatment process and tested the concentrates for mutagenicity in bacterial cells. Nonvolatile mutagens were produced by chlorination and could be destroyed by treatment with sulfur dioxide. Concentrates from unchlorinated water were found not to be mutagenic in bacterial cells. Related studies were conducted by Neeman et al. (1980) and by Gruener and Lockwood (1980).

These results suggest that the nonvolatile organics in drinking water (approximately 90% of the total organic content) may play a role in carcinogenesis and that chlorination may significantly increase the carcinogenic potential of the nonvolatile organics in drinking water. Future epidemiological studies should include as complete a characterization of both nonvolatile and volatile organics in drinking water as is practical.

CHAPTER III

CARCINOGENIC POTENCY OF SYNTHETIC ORGANIC CHEMICALS PRESENT IN DRINKING WATER FROM GROUND WATER SOURCES

Introduction

Table III.1 lists chemicals which are present in significant concentrations in some drinking water supplies derived from ground water. The maximum known concentrations of these chemicals and the location of these maximum levels are also presented. Although these maximum levels give some indication of the degree of ground water pollution in certain localities, these concentrations are not necessarily representative of the extent of nationwide contamination by any of these chemicals. The locations where these maximum levels are found are generally in areas where ground water has been monitored fairly extensively. In many other areas of the U.S., ground water has not been thoroughly monitored. Thus, data are not available for a comprehensive determination of the magnitude of the national ground water contamination problem.

Evidence of Carcinogenicity

Table III.1 also presents a summary of the evidence available at present on the carcinogenicity of these chemicals. For two of the chemicals - benzene and vinyl chloride - there is evidence of carcinogenic effects in humans from epidemiologic studies (Tomatis, 1979). Human data are not available for the other chemicals, although fourteen of the remaining twenty-nine chemicals have been

tested for carcinogenicity in animal bioassays. The animal data for 1,1,1-trichloroethane are negative and the data for 1,1-dichloroethane and parathion are suggestive only. The remaining eleven chemicals are considered carcinogenic in at least one animal species. These classifications are based upon the original investigators' judgements with regard to carcinogenicity.

Two types of classification errors - "false positives" and "false negatives" - are possible in the determination of the carcinogenicity of a chemical. In a typical animal bioassay, cancer incidences in animals exposed to various levels of a chemical are compared to cancer incidences in a control group. In order to have the best chance of detecting a carcinogenic effect, generally one group of animals is exposed to the maximum tolerated dose - the highest dose that is not estimated to produce minimal signs of acute or subchronic toxicity, such as alteration of normal longevity. Usually data are collected at a number of potential tumor sites and a study may include animals of both sexes and more than one species. Thus there are a large number of possible comparisons between control and treated animals; some of these comparisons might show a statistically significant elevation in cancer incidence in a treated group purely by chance, even when the chemical is innocuous. Generally, the determination of whether a chemical is carcinogenic is not made solely upon the finding of statistical significance but incorporates corroborative biological information as well.

Negative findings are also subject to error. By the very nature of the decision-making procedure, a study is not declared positive unless there is convincing evidence of a carcinogenic effect. With any such finding it is possible that the chemical tested was carcinogenic, but at a potency so low that the bioassay was not able to detect an effect.

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TABLE III.1

SOME SYNTHETIC ORGANIC CHEMICALS DETECTED IN WELLS USED FOR DRINKING WATER[a]

CHEMICAL	NIOSH REGISTRY NO.	MAXIMUM CONCENTRATION (µg/liter)	LOCATION	EVIDENCE FOR CARCINOGENICITY[b]
Benzene	CY1400000	230	New Jersey	H
α-BHC (α-Hexachlorocyclohexane)	GV3500000	6	California	CA
β-BHC	GV4550000	3.8	California	NT
γ-BHC (Lindane)	GV4900000	22	California	CA
Bis (2-ethylhexyl) phthalate	TI0350000	170	New York	NT
Bromoform	PB5600000	20	Delaware	NT
Butyl benzyl phthlate	TH9990000	38	New York	NT
Carbon tetrachloride	FG4900000	400	New Jersey	CA
Chloroform	FS9100000	490	New Jersey	CA
Chloromethane	PA6300000	44	Mass.	NT
Cyclohexane	GU6300000	540	New Jersey	NT
DBCP (Dibromochloropropane)	TX8750000	137	Arizona	CA
Dibromochloromethane	PA6360000	55	New York	NT
1-1, Dichloroethane	KI0175000	7	Maine	SA
1-2, Dichloroethane	KI0525000	100	New Jersey	CA

[a] List of chemicals, maximum concentrations and locations compiled by staff of Council on Environmental Quality (CEQ).

[b] CODE:
H-confirmed human carcinogen
CA-confirmed animal carcinogen
SA-Suggestive animal carcinogen
NA-negative evidence of carcinogenicity from animal bioassay
NT-not tested in animal bioassay

TABLE III.1 (Continued)

CHEMICAL	NIOSH REGISTRY NO.	MAXIMUM CONCENTRATION	LOCATION	EVIDENCE FOR CARCINOGENICITY
1-1,Dichloroethylene	KV9275000	280	New Jersey	NT
1-2,Dichloroethylene	KV9360000	323	Mass.	NT
Di-n-butyl phthlate	TN0875000	470	New York	NT
Dioxane (1-4, Dioxane)	JG8225000	2100	Mass.	CA
EDB (ethylene dibromide) (1-1,Dibromoethane)	KH9275000	300	Hawaii	CA
Isopropyl benzene	GR8575000	290	New Jersey	NT
Methylene chloride	PA8050000	47	New York	NT
Parathion	TF4550000	4.6	California	SA
PCE (Tetrachloroethylene)	KX3850000	1500	New Jersey	CA
Toluene	X55250000	260	New Jersey	NT
1,1,1-Trichloroethane	KJ2975000	5100	New York	NA
1,1,2-Trichloroethane	KJ3150000	20	New York	CA
TCE (Trichloroethylene)	KX4550000	27,300 14,000	Penn. Penn.	CA
Triflurotrichloroethane	KJ3975000	135	New York	NT
Vinyl Chloride	KU9625000	50	New York	H, CA
Xylene	ZE2100000	300	New Jersey	NT

Thus, a negative finding does not establish safety, but only determines an upper limit to the possible carcinogenic potency of the chemical in the animals tested. Chemicals which are more acutely toxic must be tested at relatively lower doses. This implies that for a given level of carcinogenic activity, a false negative finding is more likely for a more highly toxic chemical.

Once a chemical which has been found to be carcinogenic in an animal species, its human carcinogenicity must be assessed. Of 14 chemicals considered by a working group of the International Agency for Research on Cancer (IARC) to be human carcinogens (IARC, 1980), 10 were judged to have sufficient evidence of animal carcinogenicity, 2 were judged to have limited evidence for animal carcinogenicity and 2 were judged to have inadequate evidence to show either carcinogenicity or noncarcinogenicity in aminals. The IARC report stated:

> . . . In the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity (i.e., a causal association) in animals as if they presented a carcinogenic risk for humans. The use of the expressions "for practical purposes" and "as if they presented a carcinogenic risk" indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a scientific basis, but rather only pragmatically, with the intent of helping regulatory agencies in making decisions related to the primary prevention of cancer.
>
> (IARC, 1980)

This assumption has been adopted by numerous scientific groups. The National Academy of Sciences Safe Drinking Water Committee, for example stated:

> Effects in animals, properly qualified, are applicable to man. This premise underlies all of experimental biology and medicine, but because it is continually questioned with regard to human cancer, it is desirable to point out that cancer in men and animals is strikingly similar. Virtually every form of human cancer has an experimental counterpart, and every form of multicellular organism is subject to cancer, including insects, fish and plants. Although there are differences in susceptibility between different animal species, between different strains of the same species, and between individuals of the same strain, carcinogenic chemicals will affect most test species; and there are large bodies of experimental data that indicate that exposures that are carcinogenic to animals are likely to be carcinogenic to man, and vice versa.
> (NAS, 1977, p. 53)

Uncertainties in Quantitative Estimates of Carcinogenic Risks

To estimate the human risk posed by a chemical in drinking water, one needs not only evidence of its carcinogenicity, but also estimates of its potency in humans and of the concentrations to which humans are exposed. In the remainder of this chapter we consider the possible ranges of carcinogenic potencies of the chemicals in Table III.1. In the following chapter, potency estimates are combined with concentrations in drinking water from various ground water

sources to determine possible ranges of carcinogenic risks to various populations that drink ground water.

The quantitative estimation of the carcinogenic potency of a chemical in humans is more uncertain than a qualitative prediction that the chemical is carcinogenic to humans. This is particularly so when quantitative estimates are made from animal data. Such estimates involve two steps: 1) Use of animal data collected at high exposure levels to estimate the risk to animals at the (typically much lower) concentrations found in contaminated ground water (This step is frequently called "low dose extrapolation.") and 2) conversion of the animal risk estimates to estimates of human risks. The low dose extrapolation step is accomplished by fitting a mathematical dose response model to the data and determining the range of risks predicted by the model at the low concentrations of interest. Although the shape of the dose response curve at low doses greatly affects the estimated risks, mechanisms of carcinogenesis are currently not well enough understood to predict with certainly the true low dose curve shape. Current scientific views on this issue range from, on the one hand, the possible existence of a threshold of exposure below which there is no carcinogenic risk at all to, at the other extreme, the view that for many carcinogens the incremental carcinogenic risk due to the exposure is approximately proportional to dose at low dose levels (i.e., varies linearly with dose). There seems to be wide agreement among scientists that the low dose risks are likely to fall within these bounds.

After estimates are made of incremental cancer risks to animals from low concentrations, the next step is to convert these estimates to estimates of human risk. There are many physiological and biochemical differences among species which might affect the sensitivity of a given species to a

particular carcinogen. Included among these are differences in size, lifespan, metabolism, and storage and excretion rates. Metabolic differences between species encompass not only differences in rates but also differences in pathways - the chemical breakdown products themselves may be different.[8]

Another important difference between human exposures and laboratory animal exposures is that humans are simultaneously exposed to a wide mixture of chemicals rather than to a single agent. The diverse compounds ingested, inhaled, or absorbed by humans interact metabolically so that the presence of one compound may change the rates and pathways by which another is metabolized. Certain chemicals may act synergistically (e.g., cigarette smoking and asbestos exposure, Selikoff et al., 1968) to multiply the cancer risk increase produced by either separately. Relatively little is known at present concerning the prevalence or magnitude of such effects in general. Most animal studies are not designed to study synergistic effects. Human populations, being much more genetically heterogeneous than inbred laboratory strains, may also exhibit considerably greater variations in susceptibilities to carcinogenic agents.

The current theoretical understanding of carcinogenesis offers little guidance regarding the appropriate procedures for accounting for such interspecies differences when making

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[8]A recent review by Purchase (1980) compares carcinogenicity data on 250 chemicals, each of which was tested in two species (usually rats and mice). Of these chemicals 44% were classified as carcinogenic in both species, 38% in neither species, and 17% were in disagreement. The author observes that extrapolation from animals to man is another form of interspecies comparison and concludes that such extrapolation may be subject to substantial errors when based on only a single-species animal study.

quantitative risk estimates. Typically, it is assumed that animals and humans are generally equally susceptible to a given lifetime dose, with dose measured in particular units. Units of dose which have been suggested for this purpose include: 1) mg/kg body weight/day (weight basis), 2) ppm (parts per million) in diet, 3) mg/m^2 surface area/day (surface area basis) and 4) mg/kg body weight/lifetime. Table III.2 furnishes doses measured in units of ppm, mg/m^2/day and mg/kg/lifetime which are equivalent to a dose of 1 mg/kg/day in various species. The entries in this table simply reflect average weights, average rates of food consumption, average lifespans and average surface areas of these species.[9] As an example of the use of Table III.2, if low dose human risks are estimated from rat data using a linear model, then the mg/kg/lifetime conversion procedure yields human risks which are (25,500)(16.7)/[(730)(46.7)] = 12.5 times larger than would be obtained using the ppm conversion procedure. For each of the 4 animal species represented in Table III.2, conversion of animal risks to human risks using the mg/kg/day conversion procedure yields the lowest estimates of human risks, the ppm procedure yields higher estimates, the mg/m^2/day procedure yields still higher estimates, and the mg/kg body weight/lifetime procedure yields the highest estimates of all. The greatest range of estimates of human risks associated with these conversion factors is 40-fold and occurs in connection with mouse data; if low dose human risks are estimated from mouse data using a linear model, then the mg/kg/lifetime procedure yields risks 25,500/639 = 40 times greater than would be obtained using

[9]Average surface areas were not actually used in calculating the entries in Table III.2 but were assumed to be proportional to the 2/3 power of the average body weights of the species.

TABLE III.2

EQUIVALENT DOSE RATES

	MEASURE OF DOSE RATE			
SPECIES	(a) mg/kg body weight/day	(b) ppm in diet	(c) mg/m^2 body surface/day	(d) mg/kg body weight/lifetime
Mouse	1	5.0	3.0	639
Hamster	1	12.5	4.1	480
Rat	1	16.7	5.2	730
Dog	1	40.0	19.4	3,650
Man	1	46.7	37	25,500

Source: Crump and Howe (1980)

the mg/kg/day procedure.

One approach for assessing the appropriateness of these procedures comes from the limited number of chemicals which have been studied in animal bioassays and for which human epidemiological data are available. The National Academy of Sciences study on pest control (NAS, 1975) gave data on five[10] substances for which carcinogenic potencies could be estimated for both humans and an animal species. From these data Crump and Howe (1980) calculated ratios of carcinogenic potency in animals to potency in humans using the four dose scaling procedures. If the data from the most sensitive species are used, the animal-human correlations appear to be slightly better when the mg/kg/day scaling procedure is used; all five of the estimates of potency made from animal data are then within about an order of magnitude of those made directly from human data. Crouch and Wilson (1979) recently made a similar study of carcinogenic potencies using animal-human data on 15 chemicals. Based upon these data, they also considered that the mg/kg/day conversion procedure gave the best correlations between carcinogenic potencies of these chemicals in animals and humans. It must be recognized that the data base supporting these conversion procedures is weak and no single procedure gives uniformly better correlations between animal and human data. Since (as we shall see presently) we wish to define "plausible upper limits" to human risk, we shall use the more conservative surface area conversion procedure, which yields risks which are greater by factors of 37/5.2 = 7.1 (based upon rat data) or 37/3 = 12.3 (based upon mouse data) than

[10] Although they give data on six chemicals, it is only possible to calculate a crude upper limit to the carcinogenic potency of diethylstilbestrol in humans. The remaining five chemicals are benzidine, chloronaphazine, aflatoxin B^1, vinyl chloride and cigarette smoke.

would be obtained using the mg/kg/day conversion procedure. Using the surface area procedure, the 95% upper statistical confidence limits on the carcinogenic potencies made from animal data exceed those best estimates made from human data for all 5 chemicals considered by NAS. These studies of human-animal correlations in carcinogenic potencies indicate it is possible to make at least crude estimates of the risk to humans from animal data.

Estimates of Carcinogenic Potency

In this section estimates are presented of risks from lifetime consumption of water containing each of the chemicals listed in Table III.1 as carcinogenic or suggestive of carcinogenicity. Estimates for benzene are made from human inhalation data using the method employed by EPA (1980a) for calculating a water quality criteria level for benzene. Risk estimates for the remaining 14 chemicals are made from animal data. Each of these estimates is made from the species-sex-tumor site category which provided the largest estimate of low dose risk. Of the 15 chemicals listed in Table III.1 as carcinogenic or suggestive of carcinogenicity, 12 of the chemicals (all but benzene, α-BHC and vinyl chloride) have been tested in the bioassay program conducted by the National Cancer Institute (NCI). For these 12 chemicals estimates of human risk are made from the NCI bioassay data. The NCI bioassays all involved both sexes of two species - rats and mice. Because similar protocols were employed in these studies, their use should provide a balanced view of the relative carcinogenic potential of these chemicals. In each of the NCI bioassays the route of administration was either by gavage (insertion of the chemical directly into the stomach through a tube) or by

consumption of food mixed with the chemical. Studies using these methods of exposure should be more appropriate for estimating risks from drinking water than those for which exposure is by other routes such as inhalation or injection.

In some of the experimental studies the treatment was terminated prior to the end of the study. In other cases the treated animals were sacrificed at ages less than their average natural lifespans. Both of these situations tend to lessen the observed carcinogenic effect. Adjustments were made to the data to account for this tendency. The exact nature of these adjustments are described in the Technical Annex.

Extrapolation of animal risks to low doses was carried out using both the multistage model and the one-hit model of cancer (Crump, 1980). The multistage methodology furnishes upper statistical confidence limits on risks at low doses assuming a linear relationship between dose and cancer incidence at low doses and a possible nonlinear relationship at higher doses. EPA recently adopted this procedure for calculating water quality criteria (EPA, 1980d). The one-hit model provides larger estimates of risk and was used previously by EPA. Upper statistical confidence limits computed from either of these models vary linearly with dose at low doses and thus, as discussed previously, can be expected to provide reasonable upper limits on risks at low doses. Further discussion of these estimation procedures is given in the Technical Annex.

Table III.3 displays upper confidence limits for human cancer risk from lifetime consumption of water containing 1 µg/liter (assuming, as was done by NAS, 1977 that a human weighs 70 kg and consumes 2 liters of water per day) and based upon the multistage model. To determine estimates for any other concentration it is only necessary to multiply the

appropriate entry in the table by this concentration. Table III.4 gives maximum likelihood estimates and lower confidence limits for concentration levels corresponding to various specified risk levels. For purposes of comparison, Table III.5 presents similar estimates calculated using the one-hit model.[11]

The estimates in each of these tables were based upon converting animal risks to human risks using the surface area conversion procedure which, as mentioned earlier, seems to tend toward providing exaggerated estimates of human risk. These estimates can easily be changed to correspond to any of the other animal to human conversion procedures. Estimates made from rat data may be calculated on a mg/kg/day, ppm or mg/kg/lifetime basis simply by multiplying the entries in Table III.3 by 0.14, 0.39 or 4.9 respectively. For estimates made from mouse data, the corresponding factors are 0.08, 0.76, and 3.2 respectively.[12] These same factors also apply to the estimated dose levels in Tables III.4 and III.5; only they must be divided into the table entries. To illustrate, if the animal to human conversion is made on a mg/kg/day basis, the upper 95% limit for risk from lifetime consumption of water containing 1 μg/liter chloroform is $(4.1\times10^{-6})\times(.08) = 3.3\times10^{-7}$ and the lower 95% limit on the chloroform concentration corresponding to a risk of

[11]Other models which have been suggested by Mantel, et al. (1975) and Rai and Van Ryzin (1979) would predict much different risks in many cases than the multistage or one-hit models. However, because these models do not predict linear responses at low doses, we do not consider it appropriate to use them to estimate upper limits for low dose risks.

[12]These factors are calculated from Table III.2. As an example, the factor for changing estimates based upon mouse data from a surface area basis to a mg/kg/lifetime basis is calculated as (3.0/639)/(37/25,500) = 3.3.

TABLE III.3

UPPER STATISTICAL CONFIDENCE LIMITS ON CANCER RISKS FROM LIFETIME CONSUMPTION OF WATER CONTAINING 1 μg/liter OF A GIVEN CHEMICAL[a]

CHEMICAL	95% LIMITS	99% LIMITS	SPECIES[b]	SEX[c]	TUMOR TYPE	SOURCE
Benzene	4.4×10^{-6} (point estimate)		H		Leukemia	EPA (1980)
α-BHC	3.5×10^{-6}	8.0×10^{-6}	R	M	Hepatocellular carcinoma	Ito et al. (1975)
γ-BHC	1.3×10^{-5}	1.6×10^{-5}	M	M	Hepatocellular carcinoma(pooled controls)	NCI (1977a)
Carbon Tetra-chloride	1.9×10^{-6}	2.2×10^{-6}	M	M	Hepatocellular carcinoma	NCI (1976c)
Chloroform	4.1×10^{-6}	4.4×10^{-6}	M	F	Hepatocellular carcinoma	NCI (1976b)
DBCP	2.0×10^{-4}	2.2×10^{-4}	R	M	Squamous cell carcinoma of the stomach	NCI (1978a)

[a]Calculated from the multistage model (Crump, 1980).

CODE: [b]R - Rat
M - Mouse
H - Human

[c]M - Male
F - Female
B - Both

TABLE III.3 (continued)

CHEMICAL	95% LIMITS	99% LIMITS	SPECIES[b]	SEX[c]	TUMOR TYPE	SOURCE
1-1,Dichloroethane	1.5×10^{-4}	1.9×10^{-4}	M	M	All malignant tumors	NCI (1978b)
1-2,Dichloroethane	1.0×10^{-6}	1.2×10^{-6}	R	M	Hamangiosarcoma of circulatory system	NCI (1978c)
Dioxane	3.9×10^{-7}	4.4×10^{-7}	R	M	Nasal squamous-cell carcinoma	NCI (1978d)
EDB	4.8×10^{-4}	5.4×10^{-4}	R	M	Squamous-cell carcinoma of forestomach	NCI (1978e)
Parathion	2.9×10^{-5}	3.6×10^{-5}	R	F	Adrenal cortical adenoma or carcinoma	NCI (1979)
PCE	9.3×10^{-7}	1.0×10^{-6}	M	M	Hepatocellular carcinoma	NCI (1977b)
1,1,2-Trichloro-ethane	1.6×10^{-6}	2.0×10^{-6}	M	M	Hepatocellular carcinoma	NCI (1978f)
TCE	3.0×10^{-7}	3.3×10^{-7}	M	M	Hepatocellular carcinoma	NCI (1976a)
Vinyl Chloride	4.1×10^{-6}	4.6×10^{-6}	R	B	Liver angiosarcoma	Maltoni (1977)

TABLE III.4

CONCENTRATIONS[c] CORRESPONDING TO VARIOUS LIFETIME RISK LEVELS: COMPUTED FROM THE MULTISTAGE MODEL

CHEMICAL	MAXIMUM LIKELIHOOD ESTIMATES			95% LOWER CONFIDENCE LIMITS		
	LIFETIME RISK LEVELS					
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
Benzene	23[a]	2.3[a]	0.23[a]	--	--	--
α-BHC[b]	2100	670	210	28	2.8	0.28
γ-BHC	11	1.1	0.11	7.1	.71	0.71
Carbon tetrachloride	78	7.8	0.78	55	5.5	0.55
Chloroform	31	3.1	0.31	24	2.4	0.24
DBCP	0.63	0.063	0.0063	0.50	0.050	0.0050
1-1,Dichloroethane	2.3	0.23	0.023	0.66	0.066	0.0066
1-2,Dichloroethane	130	13	1.3	91	9.1	0.91
Dioxane	350	35	3.5	250	25	2.5
EDB	.28	.028	.0028	0.21	0.021	0.0021
Parathion	250	79	25	4.2	0.42	0.042
PCE	150	15	1.5	110	11	1.1
1,1,2-Trichloroethane	190	19	1.9	60	6	0.6
TCE	420	42	4.2	330	33	3.3
Vinyl chloride	34	3.4	0.34	24	2.4	0.24

[a]Point estimates made from a linear extrapolation of human data.

[b]The maximum likelihood concentrations for α-BHC and for parathion vary as the square root of the risk level. This is because the tumor responses for these chemicals more nearly follow a quadratic function of exposure than a linear function (See Crump, 1980).

[c]In units of μg/liter.

TABLE III.5

CONCENTRATIONS[b] CORRESPONDING TO VARIOUS LIFETIME RISK LEVELS: COMPUTED FROM THE ONE-HIT MODEL

CHEMICAL	MAXIMUM LIKELIHOOD ESTIMATES			95% LOWER CONFIDENCE LIMITS		
	LIFETIME RISK LEVELS					
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
Benzene	23[a]	2.3[a]	0.23[a]	--	--	--
α-BHC	56	5.6	0.56	27	2.7	0.27
γ-BHC	11	1.1	0.11	7.1	0.71	0.071
Carbon tetrachloride	78	7.8	0.78	55	5.5	0.55
Chloroform	31	3.1	0.31	24	2.4	0.24
DBCP	0.63	0.063	0.0063	0.50	0.050	0.0050
1-1,Dichloroethane	2.3	0.23	0.023	0.64	0.064	0.0064
1-2,Dichloroethane	130	13	1.3	91	9.1	0.91
Dioxane	350	35	3.5	250	25	2.5
EDB	0.28	0.028	0.0028	0.21	0.021	0.0021
Parathion	5.2	0.52	0.052	3.6	0.36	0.036
PCE	150	15	1.5	110	11	1.1
1,1,2-Trichloroethane	66	6.6	0.66	47	4.7	0.47
TCE	420	42	4.2	330	33	3.3
Vinyl chloride	34	3.4	0.34	24	2.4	0.24

[a]Point estimates made from a linear extrapolation of human data.

[b]In units of μg/liter.

10^{-5} is 2.4/.08 = 30 µg/liter.

Risks from exposure to vinyl chloride can also be estimated from data from human occupational exposures. Based upon such data reported by NAS (1975), the lifetime risk of liver angiosarcoma from drinking water containing 1 µg/liter vinyl chloride is estimated as 2.1×10^{-8}. (The computations leading to this estimate are given in the Technical Annex.) This figure is about 200-fold lower than the corresponding upper limits for the human risk given in Table III.3. However, these human data are very crude and the estimate made from them could be considerably in error. Possible sources of error include: 1) humans were exposed through inhalation rather than through ingestion, 2) estimates of human exposure are subject to considerable error, 3) humans were exposed on average for only a fraction of their expected lifespan, and 4) the human population may not have been followed for sufficient time for the total effect of the exposure to be manifested.

Because of the uncertainties regarding the assumptions upon which the estimates in Tables III.3, III.4 and III.5 are based, they should be interpreted and used with caution. It is our view that the estimates in Table III.3 provide "reasonable upper bounds" to the human risks. This is because they are based upon 1) a model which provides a linear relationship between dose and risk at low doses (Most cancer experts agree that a linear relationship is not apt to underestimate seriously the low dose risks) and 2) the assumption that chemicals have the same carcinogenic potency in animals and humans when dose is measured in $mg/m^2/day$. (As discussed earlier, this appears to tend to make animals appear more susceptible than humans to the few chemicals for which both human and animal cancer data are available). The reason we do not present lower limits is that there is

currently no concensus regarding what might be an appropriate curve shape for lower bounds (other than the obvious but non-informative lower bound of zero). Translated into lay terms, our interpretation of the upper limits in Table III.3 is as follows: Human risks are not likely to be much larger than these upper limits. Although the true risks may well be this large, it is possible that they are much smaller - even as small as zero. A corresponding interpretation applies to the lower limits for concentrations in Tables III.4 and III.5

The maximum likelihood estimates in Tables III.4 and III.5 are presented for information purposes; we caution against either consciously or unconsciously interpreting these estimates as "about right." It must be kept in mind that even with respect to the specific model used for the calculations, generally there are values which differ by several orders of magnitude from the maximum likelihood estimates and which are nearly as "likely" as the maximum likelihood estimates.

In order to estimate human cancer risks from consumption of contaminated ground water, it is necessary to relate the estimates of carcinogenic potencies made in this chapter to concentrations found in drinking water from ground water sources. This further step is taken in the next chapter.

CHAPTER IV.

ESTIMATES OF CANCER RISKS FROM CURRENT LEVELS OF ORGANIC CHEMICALS IN DRINKING WATER FROM GROUND WATER SOURCES

Introduction

Using the estimates of carcinogenic potencies from the previous chapter, it is possible to make crude estimates of the possible ranges of carcinogenic risks from consuming ground water containing various levels of synthetic organic chemicals. However, because no comprehensive nationwide study of the extent of ground water pollution has been undertaken, it is not possible to make a comprehensive study of risks from consuming such water. Even for those ground water drinking supplies which have been studied, concentration levels have been determined for only a relatively small number of chemicals, and many of those have not been tested for carcinogenicity (See Table III.1).

National Surveys

In 1975 the National Organics Reconnaissance Survey (NORS) (EPA, 1975) analyzed water samples from 80 water utilities distributed throughout the United States, including 16 utilities that supply ground water. Samples of both raw and finished water were analyzed to determine the concentrations of six halogenated compounds. The results for raw water from the 16 utilities that supply ground water are summarized in Table IV.1. The 95% upper limits on cancer risk associated with the maximum detected levels of these chemicals are also displayed.

Drinking water from a number of cities that use ground

water sources have been tested in three EPA surveys - NORS, National Organics Monitoring Survey (NOMS (EPA, 1977) and National Organics Screening Program (NOSP) (EPA, 1980b) - to determine the concentrations of some volatile chlorinated solvents. Concentrations for 11 of these chemicals are reported in Table IV.2. It is clear from this table that the geographical distribution of these chemicals is far from uniform. For most of these chemicals, the concentration from a single water supply dominated the calculated average concentration. The estimated 95% upper limits on lifetime cancer risk associated with the estimated average concentrations of these chemicals are also displayed.

The estimated cancer risks calculated by applying the carcinogenic potencies calculated from animal data to concentration levels detected in these surveys indicate that the concentrations of the known carcinogens were not sufficiently high to cause appreciable increases in cancer risks. However, there is still uncertainty regarding the total carcinogenic risk from these ground water supplies because some of these supplies (Miami, for example) contain large concentrations of organic chemicals which have not yet been identified.

Areas of High Pollution

Ground water which is highly polluted by synthetic organic chemicals has recently been discovered in a number of localities (based on information supplied by CEQ). Well closings because of high levels of synthetic organics have occurred in widely separated areas, including California, New Jersey, Massachusetts and New York. Nassau County, New York, which is part of Long Island, is one of the areas which has been discovered to have particularly high levels of synthetic

TABLE IV.1

CONCENTRATIONS OF 6 HALOGENATED COMPOUNDS IN RAW GROUND WATER FROM 16 DRINKING WATER UTILITIES SURVEYED IN EPA's NATIONAL ORGANICS RECONNAISSANCE SURVEY (NORS)

CHEMICAL	MINIMUM QUANTIFIABLE CONCENTRATION (µg/liter)	POSITIVE LEVELS DETECTED (µg/liter)	UPPER LIMITS ON LIFETIME CANCER RISKS[b]
Chloroform	0.1 - 0.2	0.4,0.2,0.3, 5 traces[a]	1.6×10^{-6} (based upon 0.4 µg/liter)
1-2,dichloroethane	0.2 - 0.4	1 trace	4×10^{-7} (based upon 0.4 µg/liter)
Carbon tetrachloride	1.0 - 2.0	1 trace	3.8×10^{-6} (based upon 2.0 µg/liter)
Bromodichloroethane	0.2 - 0.8	none found	no data available
Dibromochloroethane	0.4 - 2.0	none found	no data available
Bromoform	1.0 - 4.0	none found	no data available

[a]A trace indicates that the chemical was detected, but at a level below the minimum quantifiable concentration.

[b]Calculated using upper 95% limits in Table III.3.

TABLE IV.2

CONCENTRATIONS COMPILED FROM THREE EPA SURVEYS (NORS, NOMS AND NOSP) of 11 CHLORINATED HYDROCARBONS IN RAW GROUND WATER OF 27 CITIES[a]

CHEMICAL	NO. CITIES SAMPLED	% POSITIVE SAMPLES	MAXIMUM LEVELS (µg/ℓ)	AVERAGE[b] LEVELS (µg/ℓ)	UPPER LIMITS ON LIFETIME CANCER RISKS FROM AVERAGE LEVELS[c]
TCE	13	30.5	125	11.4	3.4×10^{-6}
Carbon Tetrachloride	27	7.4	20	0.9	1.7×10^{-6}
PCE	27	18.5	2	0.2	1.9×10^{-7}
1,1,1-Trichloroethane	13	23.1	13	1.1	no positive data
1,2-Dichloroethane	13	7.7	0.2	0.02	2.0×10^{-8}
Trans-Dichloroethylene	13	15.4	3.3	0.3	no positive data
Cis-Dichloroethylene	13	38.5	69	5.2	no positive data
1,1-Dichloroethylene	13	15.4	0.5	0.08	no positive data
Methylene Chloride	27	3.7	4.0	0.1	no positive data
Vinyl Chloride	13	15.4	9.4	0.9	3.7×10^{-6}

[a]Based on information compiled by CEQ from EPA (1975), EPA (1977) and EPA (1980b).
[b]Averages taken over all water samples rather than over positive samples only.
[c]Calculated using upper 95% limits in Table III.3.

organics in ground water (Kim and Stone, 1980). Maximum concentrations of the most commonly found contaminants are listed in Table IV.3. Also tabulated are the 95% upper limits on cancer risks from lifetime consumption of water containing each of these chemicals at the maximum detected concentrations. As an upper limit on the risk from the consumption of water from a hypothetical well containing each of these cancer-producing chemicals at the maximum detected concentrations, we use the sum of the upper limits on risks in Table IV.3[13] which equals $7.5 \times 10^{-4} = 1/1300$. The cancer risk from the water in this hypothetical well likely represents an extreme upper limit to the risks posed by water from any single one of these 372 Nassau County wells. Although the average concentrations in these wells were not available to us, it is evident from Table IV.3 that these average concentrations were much smaller than the maximum concentrations.

The most highly polluted well of which we are aware (based on information supplied by CEQ) is near Princeton, New Jersey. Table IV.4 lists concentrations of organic chemicals found in this well and estimates of lifetime cancer risks from water contaminated at these concentrations. Summing these lifetime risk estimates yields an upper limit for lifetime risk of 1/400.

[13]Although it is not strictly valid to add upper limits, the procedure does furnish exaggerated upper confidence limits for the overall risk, provided the risks from the individual chemicals can be combined independently to produce the overall human risk. However this procedure ignores possible synergistic effects. Currently we have no data which would permit predicting the extent of such effects among these chemicals.

Discussion

In spite of the fact that a number of assumptions were made which tended to greatly inflate these risk estimates, they are still relatively small. Suppose, for example, that the excess lifetime risk of $7.5 \times 10^{-4} = 1/1300$ calculated from the Nassau County data is for bladder cancer alone. Since the current lifetime risk of bladder cancer in the U. S. is about .011 (This is obtained by dividing the number of cases of bladder cancer (35,000) discovered yearly in the U. S. by 220,000,000 and multiplying the result by 70 years.), a lifetime added risk of 7.5×10^{-4} corresponds to less than a 10% increased risk of bladder cancer.

The estimate of excess lifetime risk of 7.5×10^{-4} is based upon a hypothetical well containing concentrations of each chemical at the maximum concentration discovered in a survey of Nassau County wells. It is also based upon a procedure for estimating low dose human risks from animal data which seems to tend to produce exaggerated estimates of human risk (although the data base supporting this statement is not very strong - see Chapter III). On the other hand, only risks from chemicals known to be present in the wells, and for which positive carcinogenicity data exist, were considered in the estimate. No adequate animal carcinogenicity data are available for some chemicals present in high concentrations in Nassau County wells. In addition, chemicals present in these wells which have not yet been identified could have a significant carcinogenic effect. It is also possible that the contaminants in these wells could act synergistically to produce a total carcinogenic effect which is larger than that suggested by animal studies on individual chemicals.

Estimates of risks from carcinogens at levels typically

TABLE IV.3

ORGANIC CHEMICALS DETECTED IN
372 NASSAU COUNTY, NEW YORK WELLS[a]

CHEMICAL	PERCENT POSITIVE	MAXIMUM LEVEL DETECTED (µg/ℓ)	UPPER LIMITS ON LIFETIME CANCER RISKS[b]
PCE	15	375	3.5×10^{-4}
TCE	13	300	9.0×10^{-5}
Chloroform	11	67	2.7×10^{-4}
1,1,1-Trichloroethane	9	310	no positive data
Carbon Tetrachloride	5	21	4.0×10^{-5}
Triflurotrichloroethane	1	135	no positive data

[a]Source: Kim and Stone (1980).

[b]Calculated using upper 95% limits in Table III.3.

TABLE IV.4

ORGANIC CHEMICALS DETECTED IN A HIGHLY POLLUTED NEW JERSEY WELL[a]

CHEMICAL	CONCENTRATION (µg/ℓ)	UPPER LIMITS ON LIFETIME CANCER RISKS[b]
TCE	1530	4.6×10^{-4}
Trichloroethane	965	1.3×10^{-4}[c]
Chloroform	420	1.4×10^{-4}
Carbon Tetrachloride	400	7.6×10^{-4}
Xylenes	300	no positive data
Toulene	260	no positive data
Benzene	230	1.1×10^{-3}
Dichloroethylene	58	no positive data
Methylene Chloride	11	no positive data

[a]Based on information supplied by CEQ.

[b]Calculated using 95% upper limits in Table III.3.

[c]This assumes the 1,1,2-Trichloroethane isomer.

found in chlorinated surface water (e.g., typical of levels reported in NORS) correspond to risk ratios far below the ratios found by the five epidemiological case control studies in Chapter II. It is worth examining this point in some detail because of its potential implications regarding the direction of regulatory policy and future research.

The NORS Survey (EPA, 1975) tested water in 10 cities for the presence of 129 organic chemicals. The concentrations of the nonTHMs were quite low compared to the concentrations of chloroform. When the concentrations of the nonTHM carcinogens are multiplied by the carcinogenic potencies in Table III.3 and the resulting risks are added, the total risk is still negligible compared to the estimated risk associated with chloroform. The risks associated with the other three THMs cannot be estimated because no animal data are yet available. To compute the risk associated with chloroform we will assume a chloroform concentration of 45 µg/liter. (This is the average of the cholorform concentrations in the 80 chlorinated water supplies survey in NORS and is higher than the median value of 21 µg/liter reported for these sources.) Next we multiply by the value of 4.1×10^{-6} from Table IV.3, which is the 95% upper limit for the lifetime total cancer risk in man from drinking 2 liter/day of water with a chloroform concentration of 1 µg/liter. This yields an upper limit for the lifetime increased cancer risk of $45 \times 4.1 \times 10^{-6} = 1.8 \times 10^{-4}$.

In summary, we view the human cancer risk from drinking water as being due to the combination of three quantities: 1) a chloroform-associated risk estimated on the basis of animal data to be no greater than 1.8×10^{-4}, 2) a risk which is calculated by summing all risks associated with identified nonTHMs, the total of which is negligible compared to the chloroform risk, and 3) an unknown risk associated

with a) the three other THMs for which carcinogenicity data are not yet available and b) the as yet unidentified organic compounds in drinking water. According to the National Academy of Sciences (NAS, 1977), about 90% of the total organic content in drinking water is not yet identified.

Taking the chloroform-associated risk as the total increased cancer risk and assuming that this is reflected entirely as rectal cancer cases, we can compare this to the lifetime human rectal cancer risk of roughly 1.11×10^{-4} computed by dividing the approximately 35,000 newly diagnosed rectal cancer cases in the U. S. each year by the U. S. population of 220 million and multiplying by 70. This yields a risk ratio of $(1.8 + 1.11)/1.11 = 1.02$, which is much lower than the ratios of 1.13 to 1.93 found in case control studies discussed in Chapter II and is almost certain to be too low to be detected by epidemiologic methods. This same conclusion was also reached by Pike (1980). We can think of four possible reasons why the estimates made from animal data lie considerably below those generally suggested by the epidemiological studies.

1. <u>The positive findings of the case control studies are influenced by confounding so that they overestimate human risks</u>.

The case control studies completed to date have found risk ratios of from 1.13 to 1.93 for rectal cancer and even smaller risk ratios for colon and bladder cancer. Risk ratios which are this small are subject to question no matter how large the study. There are many potential sources of confounding and bias which may cause spurious effects of this magnitude. Two of the five studies did not find the elevations in rectal cancer risk ratios to be statistically

significant. In these studies the lower confidence limits on the risk ratios are less than one. The risk ratio of 1.02 inferred from animal data is thus fully compatible with the rectal cancer risk estimates from these two studies. On the other hand, the consistent findings of increased risk ratios for rectal cancer in 5 separate studies decreases the likelihood that these findings are all due to confounding. These studies do attempt to control for age, sex, race, urbanization occupation and (to some extent) migration. The lack of detailed individual exposure histories should make the studies somewhat less likely to detect true effects, but should not greatly increase their propensity to yield false positive associations.

2. A marked synergism among organic contaminants may be present.

We have noted earlier that certain chemicals may act synergistically to produce carcinogenic effects which are greater than the sum of the effects from each chemical considered separately. Animal bioassay data which would permit estimation of synergistic effects of chemicals in ground water are not available. Comparisons of the mutagenic activity of organic extracts from drinking water with the corresponding activity produced by some of the individual constituent chemicals might provide some clues about the degree of synergism among the organics in drinking water.

3. Estimates of human carcinogenic potency based on animal data may be far too small.

In making these human potency estimates we made a number of assumptions which should tend to yield exaggerated

estimates of human potency. We calculated upper 95% confidence limits from a dose response model which is linear at low doses. We used data from the most sensitive tumor site of the more sensitive sex of the most sensitive strain, and we converted animal risks to human risks based on the surface area method. Current evidence suggests that this estimation procedure is likely to overstate human risks. Others have argued that these procedures should greatly overstate human risk.

4. Most of the increased human risk from chlorinated water is due to organic chemicals not yet identified or for which data are not available.

About 90% of the total organic content of drinking water consists of nonvolatile compounds, of which only about 5% to 10% have been identified (NAS, 1977). It seems very plausible that this unidentified fraction could be posing a significant carcinogenic risk to humans - a risk that is not accounted for in the estimates from animal data made in this chapter. Nonvolatile organic concentrates from drinking waters of several U. S. cities have been shown to be mutagenic in bacterial assay systems and to be capable of transforming cultured mouse fibroblasts into cells exhibiting properties of tumor cells (Loper, et al., 1978). Chlorination has been shown to greatly increase the mutagenicity of nonvolatile organics in drinking water (Cheh et al., 1980). These results suggest that appreciable carcinogenic risks may indeed be associated with the nonvolatile compounds in drinking water.

Similarly, the THMs bromodichoromethane and chlorodibromomethane, which were detected in the drinking water of 78% and 72%, respectively, of the utilities surveyed

in NORS and which have not been tested for carcinogenicity, have both been shown to be mutagenic in the Ames Salmonella assay (Simmon and Tardiff, 1978). Chloroform was also tested for mutagenicity by Simmon and Tardiff and found to be negative. This suggests that bromodichloromethane and chlorodibromomethane could possibly be more highly carcinogenic than chloroform. If this is true, the carcinogenic potential of the total THMs in drinking water might be considerably greater than that from chloroform alone.

Thus it seems entirely possible that an appreciable human cancer risk from chlorinated water could be due to the nonvolatile organic content of drinking water - the composition of which is largely unknown - and to volatile organic contaminants which are frequently present in significant amounts in chlorinated water but which have not been tested for carcinogenicity. This seems to us to be the most plausible explanation for why the increased risks inferred from epidemiological studies are higher than those extrapolated from animal data on the carcinogenicity of individual chemicals.

CHAPTER V
SUMMARY AND CONCLUSIONS

Epidemiological case control studies relating water quality to cancer risk have found rectal cancer risks associated with chlorinated water to be a factor of 1.13 to 1.93 higher than those associated with unchlorinated water. In three of the five studies the elevation in the risk ratio was statistically significant at the 5% level. Colon cancer risk ratios also exhibited statistically significant elevations in three of the five studies as did bladder cancer risk ratios in two of the studies. Increased risks of rectal, bladder and colon cancer of the magnitudes suggested by these studies are large enough to be of concern but yet small enough to be very difficult to separate from confounding risks associated with other environmental factors.

Three of these studies investigated dose response effects by attempting to determine whether there were increasing cancer risks with increasing exposure to organic contaminants in drinking water. No clear trend was established. One study showed increasing rectal cancer mortality rates with increasing exposure to surface water. This suggests a dose response gradient for rectal cancer. In another study results suggestive of a colon cancer dose response gradient were found when effects of water purification and rural runoff were taken into account.

A central issue related to the review of these studies is the type and extent of additional evidence which must be forthcoming before it can be determined whether synthetic organic contaminants in drinking water <u>cause</u> human cancer. This subject was discussed in Chapter II using as a

conceptual framework the well-known criteria of Sir Bradford Hill (1965) for judging causality on the basis of scientific evidence. While the epidemiological studies completed to data are not sufficient to establish a causal relationship between chlorinated organic contaminants in drinking water and cancer, they do contain evidence which supports such a relationship for rectal cancer and to a lesser extent for bladder and colon cancer. The recently completed case control studies have strengthened the evidence for an association between rectal, colon and bladder cancer and drinking water quality provided by the earlier epidemiological studies reviewed by the National Academy of Sciences committee (NAS, 1978, 1980).

The methodologies used in these case control studies represent a considerable refinement over those used in the earlier ecological studies. Linkage of individual residential addresses with their water supplies permitted improved measures of exposure. In all but one of the case control studies, migration was controlled for either by selecting study population from areas with low rates of migration during the past 20 years, or else by using indirect measures of migration based upon place of birth and place of death. The occupations listed on the death certificates were used in some of the studies to control for possible confounding due to occupation. The study of Kanarek and Young (1980), which found a statistically significant association between colon cancer and drinking water quality, was limited to white females, only 0.56% of whom were employed in an occupation considered to have a high cancer risk. All but one of the studies controlled for age, race, and sex. Gottlieb et al. (1980a,b) also controlled for ethnic background (Acadian ancestry).

However, these case control studies have some of the

same limitations as the earlier ecological studies. The measures of water quality used in the case control studies are essentially the same indirect measures that were used in the earlier ecological studies. Use of death certificate data limits the information available to evaluate potentially confounding factors. Dietary and smoking habits are not a part of death certificate data. Death certificates only include a recent residential address and the "usual" occupation; detailed residential and occupational histories are generally not available. The latency period between exposure to a carcinogen and diagnosis of cancer is probably at least ten years for gastrointestinal and urinary tract cancer. Thus the water qualities which should be correlated with increased cancer risks in these studies are those to which the subjects were exposed at least ten years (and probably longer) prior to their deaths. None of the studies completed to date include direct measurements of water quality during this time period.

Future work is needed to measure risks in study populations with known exposure histories and with a large enough number of cases and controls to permit accounting for potentially confounding effects of other environmental factors such as diet (including types of food eaten, coffee and alcohol comsumption, artificial sweetener comsumption, and medications taken), smoking, air pollution, occupation, proximity to industrial sites, and previous radiation therapy. Based on epidemiological studies conducted to date, such a study should be large enough to detect risk ratios of around 1.30. As can be seen from Table V.1, this would likely require over 1000 cases at each site.

In addition, future studies should be designed to be capable of measuring a trend of increasing cancer risk with increasing duration and intensity of exposure to contaminated

TABLE V.1

CASES REQUIRED FOR CASE CONTROL STUDIES[a]

RELATIVE RISKS TO BE DETECTED	FRACTION f OF POPULATION EXPOSED TO RISK FACTOR											
	f=0.5				f=0.3				f=0.15			
	RATIO OF CONTROLS TO CASES				RATIO OF CONTROLS TO CASES				RATIO OF CONTROLS TO CASES			
	K=1	K=2	K=4	K=8	K=1	K=2	K=4	K=8	K=1	K=2	K=4	K=8
1.1	6994	5246	4372	3934	8168	6111	5082	4568	13,260	9902	8222	7382
1.2	1936	1453	1211	1089	2222	1659	1377	1236	3559	2647	2191	1962
1.3	947	711	592	533	1069	797	661	592	1691	1254	1035	925
1.4	583	438	365	328	649	483	400	358	1014	750	617	550
1.5	407	306	255	229	446	332	274	245	689	508	417	371
1.6	306	230	192	173	332	246	203	182	507	373	305	271
1.7	243	183	153	137	260	193	159	142	394	289	236	209
1.8	201	151	126	113	212	157	130	116	318	233	190	168
1.9	170	128	107	96	178	132	109	97	264	193	157	139
2.0	148	111	93	84	153	113	93	83	225	164	133	118

[a]This table shows the approximate number of cases required to detect a given odds ratio in a case control study, assuming a significance level of 0.05 (two sided test) and a power of 0.80. The number of controls required is determined by multiplying the number of cases by the ratio of controls to cases. The numbers are calculated using Schlesselman (1974) and Fleiss et al. (1980). (Specifically, equations (3) and (4) of Fleiss et al. (1980) are used with the parameters P_1 and P_2 of equation (4) being replaced by f and P_3 respectively of Schlesselman (1974), equations (3) and (4)). The numbers above do not include any increased sample size requirements caused by the need for stratification.

water. The case control studies to date have been able to establish some suggestion of dose-response effects in certain cases where sufficient information was available to control for factors such as migration, rural runoff, and water purification. Future case control studies based on interview data should have sufficiently detailed exposure histories to permit more detailed study of dose-response trends. The appreciable variations in chloroform levels noted by Hogan et al. (1979), on the same drinking water sources measured several months apart, suggest that seasonal variability in organic contamination levels may make it quite difficult to establish unequivocal dose response trends.

The effect of this large temporal variation is magnified by the latency period of over 10 years between initiation and diagnosis of cancer. Newly diagnosed cancer cases should be correlated with measures of water quality applicable to their residencies throughout the latency period.

Another basic difficulty in attempting to establish dose-response trends has to do with the use of indirect measures of exposure. Chlorination dose or even trihalogenated methane content may not be a reliable indicator of the carcinogenic potential of all of the organic material in drinking water. More detailed direct measures of organic and other water contaminants such as nitrates, heavy metals, and radionuclides should be considered in attempting to detect dose-response trends.

In summary, available evidence indicates that the putative cancer risks associated with drinking water lie near the limits of detectability by large well-designed epidemiological studies.

A large case control study of bladder cancer is now being conducted by Cantor, et al. under the sponsorship of the National Cancer Institute. This study is based on

interview data from 3000 cases of bladder cancer newly diagnosed in 1978, and from 6000 controls. As discussed in Cantor, et al. (1980), information was obtained on demographic background, medical history, smoking history, occupational history, artificial sweetener use, coffee drinking, use of hair dyes, fluid ingestion patterns, lifetime residential history, and lifetime water source history. An information bank on water quality has been created for more than 1000 utilities serving many of the people in the study. This information should permit individual exposure to many potential bladder cancer risk factors to be linked to individual risk of disease. It would appear that this study may have the capability of detecting risk ratios associated with chlorinated water of about 1.20.[14] In addition, a study of colorectal cancer is being conducted by Shy and Struba based on interview data from about 450 cases and about 900 controls. Use of interview data should permit controlling for a number of potentially confounding variables which have not been adequately controlled for in the studies to date based on death certificate data.

Numerous incidents have recently occurred in which drinking water from ground water sources has been found to be contaminated with synthetic organic chemicals at concentrations far above those seen in surface water or ground water in previous national surveys. These contaminants - consisting of trihalogenated methanes, pesticides, industrial solvents and other organic chemicals - include many known or suspected human or animal carcinogens. The pollution of

[14]This is based on the estimated sample sizes shown in Table V.1. These estimates do not allow for any changes in sample sizes caused by the need to stratify.

ground water is of concern not only because of present health risks, but also because once contaminated, ground water may remain so for decades. The epidemiological studies completed to date do not permit estimation of risks due to these recently identified organic contaminants in unchlorinated drinking water from ground water sources. In fact, in these studies unchlorinated ground water was taken as a standard of unpolluted water against which water from other sources was judged.

To estimate risks from chemicals present in ground water, a list of chemical carcinogens known to be present in significant quantities in drinking water wells was compiled. Carcinogenic potencies were estimated for each of these chemicals based upon data from animal bioassays. This was a two-step procedure. First, low dose carcinogenic potencies were estimated from animal data using a method recently adopted for this purpose by the EPA (1980d). Next these animal risk estimates were converted so as to apply to humans using a method based on the relative surface areas of the animal species and humans. These calculated carcinogenic potencies were then used to estimate an upper limit on human risk for each single chemical at the maximum concentration known to be present in drinking water wells in one of the most highly contaminated areas of the country. Finally, all of the risks were added together to estimate an upper limit of the risk from all of the carcinogens identified in these wells. The resulting estimate of lifetime human excess risk was less than 0.1%. Since the national lifetime cancer risks for rectal, colon and bladder cancer are each at least 1%, a lifetime risk of 0.1% would correspond to less than a 10% increase in human cancer risk at any one of these cancer sites.

There are many uncertainties associated with these

estimates. The low dose animal potencies were estimated by upper confidence limits calculated from a multistage model which assumes that risk increases linearly with dose for low doses. This procedure is probably more apt to overestimate than underestimate low dose risks. If the linear assumption is not valid, this procedure might greatly overestimate risks from low doses. The procedure used for converting from animal risks to human risks also seems, on the basis of human-animal comparisons made from other chemicals, to tend to overestimate human risks. However, the data base upon which these human-animal comparisons are made is weak.

On the other hand, only chemicals which have been identified as ground water contaminants and for which adequate carcinogenicity data exist were accounted for in the risk estimates for these highly polluted wells. High concentra- tions of other chemicals were present which have not been adequately tested for carcinogenicity and, further, chemicals which have not yet been identified could have a significant carcinogenic effect. It is also possible that the contaminants in these wells could act synergistically to collectively produce a carcinogenic effect which is larger than that suggested by animal studies on individual chemicals. No data were available that would permit the possibility of such synergistic action to be taken into account in the risk estimate.

The NORS Survey (EPA, 1975) analyzed water samples from 80 water utilities for the presence of a number of organic compounds including the 4 THMs. When human cancer risks are estimated using the average concentrations found in these samples and animal bioassay data (applying the same procedure as described above for estimating risks from drinking water from polluted wells), the estimate of 1.8×10^{-4} is obtained for the lifetime increased cancer risk. Essentially

all of this estimated risk is due to chloroform; the remaining organic contaminants which were measured in NORS were either present in very low concentrations or have not been adequately tested for carcinogenicity in an animal bioassay. Assuming that all of this increased risk is reflected in rectal cancer cases, it is estimated that an increased lifetime risk of 1.8×10^{-4} would correspond to a risk ratio of 1.02 for rectal cancer. This ratio is lower than the ratios of 1.13 to 1.93 found in case control studies discussed in Chapter II and is almost certain to be too low to be detected by epidemiologic methods. There are several possible explanations for this.

First, the epidemiological studies may be overestimating the effect of drinking water on human cancer. The increased risk ratios found in these studies may be largely or completely due to confounding by other environmental risk factors which could not be accounted for within the limitations of present study designs. For example, differences in smoking rates among groups exposed to different levels of water quality could lead to false increases in the excess risk associated with different levels of organic contaminants in drinking water.

A second possibility is that there could be a marked synergism either among organic contaminants in drinking water or between the organic contaminants and other factors in the environment. Such a synergism would not be noted in animal tests where the animals are exposed to only one chemical agent for all of their lives. A third possibility is that humans may be more susceptable to the carcinogenicity of these chemicals than are the animal species which have been tested.

Fourth, it seems very plausible that currently unidentified chemicals in drinking water may be posing a

significant carcinogenic risk to humans - a risk that is not accounted for in estimates made from animal data. About 90% of the total organic content of drinking water has not yet been identified. This unidentified component is a complex mixture consisting mainly of nonvolatile organic compounds. Recent laboratory studies have shown that concentrates of chlorinated nonvolatile organic material obtained from drinking water can be mutagenic. This suggests that this material may be carcinogenic as well.

Summary of Major Conclusions

1. The recently completed case control studies have strengthened the evidence for an association between rectal, colon and bladder cancer and drinking water quality provided by the earlier epidemiological studies reviewed by the National Academy of Sciences committee. While the epidemiological studies completed to date are not sufficient to establish a causal relationship between chlorinated organic contaminants in drinking water and cancer, they do contain evidence which supports such a relationship for rectal cancer and, to a lesser extent, for bladder and colon cancer.
2. Putative increases in cancer risks associated with organic contaminants in drinking water appear to lie near the lower limit of what can be detected and separated from other environmental risks by a large, well-designed case control study involving over a thousand cases.
3. No clear trend of increasing risk with increasing exposure (dose-response gradient) has been demonstrated by the studies conducted to date although evidence

suggestive of such trends has been obtained for rectal cancer in one study and for colon cancer in another study.

4. Concentrates of chlorinated nonvolatile organic compounds in drinking water have been found to be mutagenic in mammalian cells and to be capable of transforming human cells into cells which exhibit some biochemical properties associated with tumor cells. These results support the hypothesis that chlorinated nonvolatile organic compounds in drinking water may be carcinogenic in humans. Most of the nonvolatile organic content of drinking water has not yet been identified.

5. Estimates made from animal data of human cancer risks from lifetime consumption of water from some highly polluted wells are small enough that they would probably not contribute noticeably to existing human cancer rates. However these estimates do not incorporate risks from a) as yet unidentified organic contaminants, b) contaminants identified in ground water but for which no adequate carcinogenicity data exist, or c) possible synergistic effects of organic contaminants in ground water.

Directions for Future Research

1. Case control studies based upon interview data from newly diagnosed cases of rectal, bladder and colon cancer are needed. Such studies should relate cancer risks to lifetime water quality histories while controlling for the potentially confounding effects of smoking, diet, coffee drinking, artificial sweetener consumption, alcohol consumption, migration, occupational history and other environmental

exposures. Water quality measurements would include as complete a characterization of the organic contaminants as practical, as well as measurements of other contaminants such as nitrates and radionuclides. At least a thousand cases at each site should be included so as to provide some assurance of detecting risk ratios around 1.3. It should be noted that a large case control study based on interview data from over 3000 newly diagnosed cases of bladder cancer and satisfying many of the above conditions is nearing completion. In addition, a case control study based on interview data from over 450 colorectal cancer cases is in progress.

2. Further studies of the identities, carcinogenicity, mutagenicity, mode of formation and practical methods of removal are needed for the organic contaminants in drinking water.

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TECHNICAL ANNEX

This annex furnishes details of the calculations reported in Tables III.3, III.4 and III.5. These calculations were similar to those used by EPA to determine water quality criteria (EPA, 1980d).

In each animal study the reported dose levels were converted to average doses in mg/kg/day, averaged over the time from the beginning of exposure until the experiment was 80% complete. The 80% figure was selected because, due to the latency period of environmentally induced cancers, exposures occurring in the last 20% of an animal's lifespan are less likely to affect the observed carcinogenic response.

A further adjustment was made to the data from experiments which terminated at a lesser time than the normal lifespan of the species. The carcinogenic effect of the chemical would likely have been greater in such studies had premature termination not occurred. To make such an adjustment, an average natural lifespan T_n was defined. For rats T_n = 730 days and for mice T_n = 639 days. If the length T of a study was less than T_n, each of the administered dose levels was multiplied by $(T/T_n)^4$. This particular adjustment is supported by studies of both human data (Doll, 1971) and animal data (Druckrey, 1967). The data from most of the studies required only minimal, if any, adjustments of these kinds.

The extrapolation procedure of Crump (1980) based upon the multistage model of cancer was used for extrapolation to low dose. This particular methodology was recently adopted by EPA for setting water quality criteria (EPA, 1980d). The method involves fitting the flexible multistage dose response

model to the experimental data and then calculating an upper statistical confidence limit q_u for the slope q of the dose response curve at low doses. The parameter q is called the carcinogenic potency of the chemical. For each chemical the multistage methodology was applied to each of the data sets which were reported in the original study as exhibiting carcinogenic effects and the data set which yielded the largest upper limit q_u was used to estimate human risks. (Each data set pertains to a given species, sex and tumor category.) For each data set analyzed, if the multistage model did not provide a satisfactory fit to the data based upon a chi-square goodness of fit test, data at the highest dose were deleted. This process was continued until a satisfactory fit was obtained.

The risk predicted by the multistage model from a low dose d is approximately qd; therefore, $q_u d$ represents an upper statistical confidence limit on lifetime animal risk from dose d where d is in units of mg/kg/day. To convert this upper limit to human risks using the $mg/m^2/day$ procedure, it was multiplied by a constant C calculated from Table III.2. For rat data C = 37/5.2 = 7.1 and for mouse data C = 37/3 = 12.3. The upper statistical limit on human risk from lifetime consumption of water containing x μg/liter of a chemical is then

$$\frac{(x\ \mu g/liter)(2\ liter/day)(.001\ mg/\mu g)\ Cq_u}{(70\ kg)} = \frac{xCq_u}{35000}$$

This is based upon a 70 kg human who consumes 2 liters/day of water.

Given a particular upper limit q_u, a lower limit on the lifetime dose in mg/kg/day producing a given risk R in animals is simply R/q_u. Therefore, a lower limit on the

concentration in water in units of μg/liter producing a given risk R in humans is

$$\frac{35000R}{Cq_u}$$

Lower limits in Table III.4 were calculated from this expression. The maximum likelihood estimates in Table III.4 were calculated by the expression

$$\frac{35000D}{C}$$

where D is the maximum likelihood estimate of the animal dose in mg/kg/day which produces the postulated risk.

These same procedures, but applied to the one-hit model (see Crump, 1980), were used for the calculations reported in Table III.5. The data used to calculate a given entry in Table III.5 was the same as those used to calculate the corresponding entry in Table III.4 and which are stated in Table III.3.

With both the multistage and one-hit models, confidence limits are linear at low doses - that is, upper confidence limits on risks from small doses are proportional to the dose level, and lower confidence limits on doses corresponding to small values of extra risk are proportional to the level of extra risk. The multistage model is a more flexible model and provides a better description of many data sets than the one-hit model. This is illustrated in Figure AI which shows the maximum likelihood fits of the multistage and one-hit models to the data from the NCI (1979) bioassay of parathion which were used in Tables III.3, III.4 and III.5. These data are exhibited in Table AII.

We consider the extrapolations from animal data based upon the multistage model (Table III.3) to be more appropriate for estimating upper limits to cancer risks than those based upon the one-hit model. Because the multistage

upper limits in Table III.3 vary linearly with the concentration level, only a simple multiplication is required to calculate an upper limit on risk from any other specified concentration level. For example, using the upper 95% risk value of 4.1×10^{-6} in Table III.3 for chloroform, an upper limit on risk from lifetime ingestion of water containing 20 µg/liter chloroform is $(20)(4.1 \times 10^{-6}) = 8.2 \times 10^{-5}$. Predictions of the overall risk from the simultaneous presence of several chemicals in drinking water are most uncertain. Crude upper limit estimates were made in Chapter IV by adding the upper limit estimates made for concentrations of the individual chemicals. (See footnote 13 for a discussion of the validity of this approach.)

The selection of data used to estimate the carcinogenic potency of 2 of the chemicals did not exactly follow our prescription and deserves special comment: 1) The summary of the NCI bioassay of 1-1,dichloroethane noted several tumor sites at which a suggestive dose-related effect was observed, but did not declare the study to be positive. The category of "all malignant tumors," which was not analyzed in the NCI report, showed a larger dose-related increase than any of the categories which were analyzed. Thus we decided to base our risk estimates upon all malignant tumors. 2) The NCI data on γ-BHC (lindane) was only suggestive of carcinogenicity, whereas the study by Thorp and Walker (1973) which used larger doses, resulted in a highly statistically significant incidence of hepatic neoplasm. We decided to estimate risks using the NCI data because the experimental protocols of this study were more compatible with those of the studies available for the other chemicals.

The estimate presented in Chapter III of the risk from vinyl chloride, which was based upon human occupational exposures, was made as follows. NAS (1975) reported an

FIGURE AI

FITS OF THE MULTISTAGE AND ONE-HIT MODELS

TO DATA IN TABLE A1

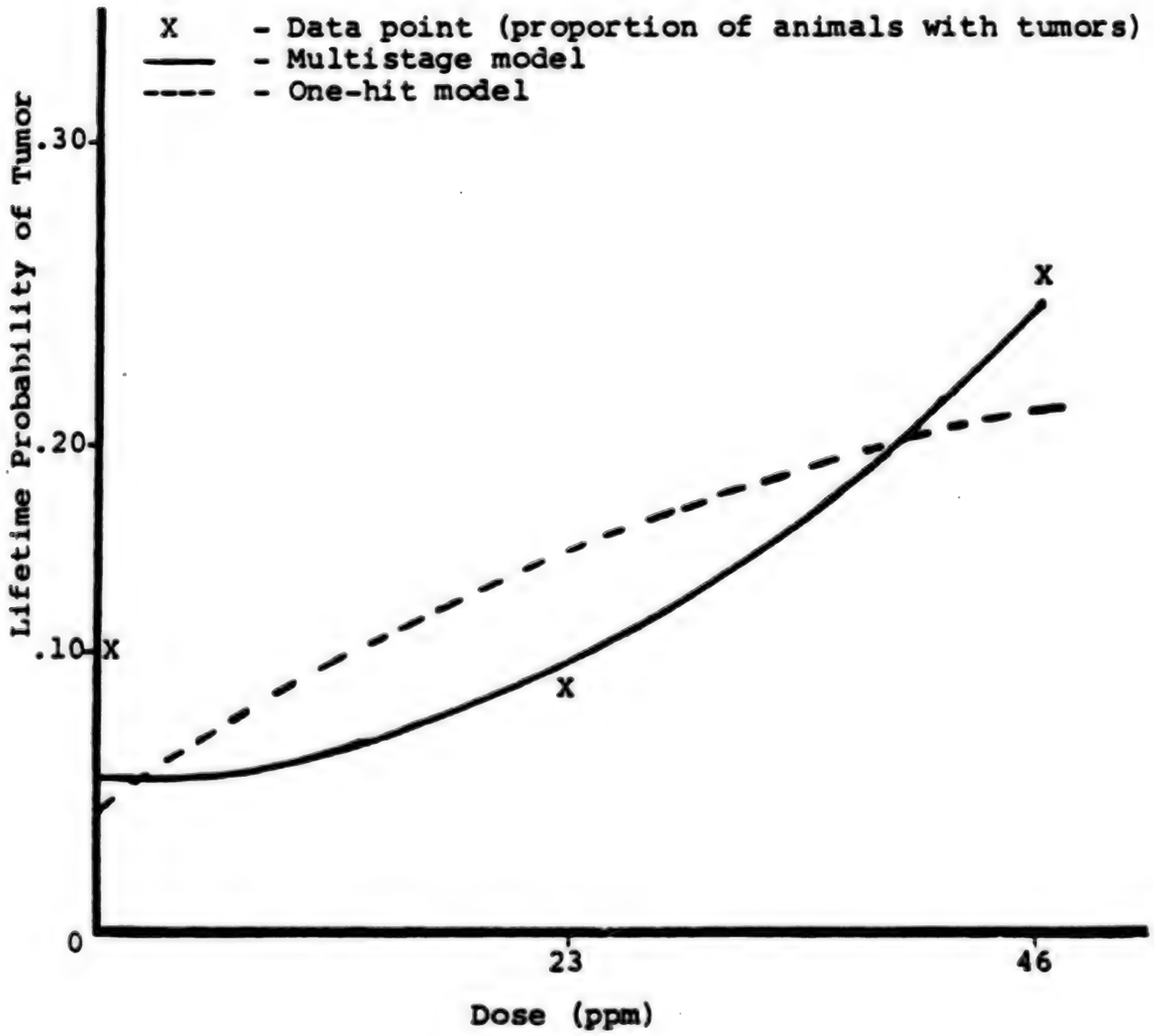

TABLE AI

INCIDENCE OF ADRENAL CORTICAL ADENOMA OR CARCINOMA IN RATS EXPOSED TO PARATHION

DOSE (ppm)	NUMBER OF ANIMALS	NUMBER OF ANIMALS WITH TUMORS
0	10	1
23	47	4
45	42	11

Source: NCI (1979)

estimate of an incidence of liver angiosarcoma of 0.2% among industrial workers from an estimated average total dose of vinyl chloride of 70,000 mg/kg. Averaged over 70 years, this dose is equivalent to 70,000/[(70)(365)] = 2.7 mg/kg/day. Considering a 70 kg man who consumes 2 liters of water per day, this same dose would result from lifetime consumption of water containing

$$\frac{(2.7\ \text{mg/kg/day})(70\ \text{kg})(1000\ \mu\text{g/mg})}{2\ \text{liters/day}} = 96000\ \mu\text{g/liter}$$

vinyl chloride. Using a linear dose response, the risk of liver angiosarcoma from drinking water containing 1 µg/liter is estimated as .002/96,000 = 2.1×10^{-8}.

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